

MODERN CONCEPTIONS IN SYPHILOLOGY WITH SPECIAL
REFERENCE TO SEROLOGICAL DIAGNOSIS AND
TREATMENT BY THE ARYLARSONATES AND BISMUTH.

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General Summary.

Section 1.

INTRODUCTION

On casting a critical eye over the modern equipment which we possess to combat disease the honest physician must be appalled by its relative uselessness and by the empiricism which is dominant nearly everywhere despite our most elaborate research and clinical apparatus. In recent years, however, a few vantage points have been won and retained by therapeutic weapons of the first magnitude, and such weapons do we possess in our struggle against the *Treponema pallidum* - weapons which if judiciously used are capable of dealing a devastating blow to one of the most universal and crippling diseases which harass mankind. In diagnostic and therapeutic agents our anti-syphilitic armoury is probably better equipped than any other, and while it would be rash to say that the arylarsonates are the highway in the evolution of the treatment of syphilis, they never-the-less form a path which has led to very satisfactory results and to a vista which is even more promising.

As Dr. Robertson has pointed out (1), it does not seem so long ago that our main defence lay in mercury and the iodides administered with a liberality or meagreness, depending solely on the inclination and character of the physician. Now added to these, we have the whole array of the arsenic and bismuth compounds which can be given in doses carefully graded and scientifically controlled;

diagnostic procedures have improved beyond measure with the discovery of the organism, the dark-ground microscopical examination and the various serological tests; nor have the Public Health authorities been slow in awakening to their responsibility, as the free and easily accessible clinics throughout the country can testify.

With the discovery of the *Treponema pallidum* in the primary sore of syphilis and thereafter in the many and varied lesions which manifest themselves in the tertiary stage, a mass of literature sprang up, which has accumulated with the increase of our knowledge in diagnostic and therapeutic methods; and it is proposed in this thesis to cull from this welter of literature the more outstanding points in the recent work, and to show how our improved knowledge of the aetiology of the disease has influenced our methods of diagnosis and treatment.

If we study the syphilitic process in its general characteristics we find that the local reaction, developing at the site of inoculation gives place after a variable interval to an acute syphilitic storm, which marks the reaction of the tissues to the generalisation of the infection, and is characterised by the well known epidermal lesions of the secondary stage, accompanied by the usual concomitants of an acute infection - fever, headache, malaise, etc. This reaction of the body easily overcomes the infection, but not completely, and although the reacting tissues develop for the time

being an immunity, the *treponema pallidum* is not exterminated, but merely becomes quiescent and lodged in "back alleys" where the comparatively slight irritation produces the fibrosis and destruction of the tertiary lesions - a reaction of tissues sensitised to the infecting organism.(2). It is not proposed here to discuss the various theories of immunity, local and general, propounded to explain these phenomena; suffice that we point out that the *Treponema pallidum* is an organism easily killed in the early generalised stage, i.e. when the protective mechanism of the body can reach it, and before it has become shut off in localised areas of sensitised organs. Now in this syphilis is not alone; many other infections have a similar characteristic of causing an acute generalised reaction on the part of the body, which for the time being is over-whelming to the organism, driving it into localised areas where it later promotes a slow chronic proliferative or destructive process often with acute generalised exacerbations. Typical examples of this clinical course may be seen in Trypanosomiasis, Yaws, Malaria, Relapsing Fever, and Kala-azar which although differing widely have this in common with Syphilis - they all have clinically a period of acute reaction followed to a greater or lesser extent by a period of quiescence.

Now it has been noted that during the initial generalised infection the causative organisms of these diseases are highly vulnerable and

we should expect therefore that many drugs would have been discovered as specific germicides in the early stages; nor should we be, as so often happens in medicine, completely disappointed; we have Quinine in Malaria, Tryparsamide in Trypanosomiasis, Antimony in Kala-azar, and the Arylarsonates and Bismuth in Syphilis. (It is interesting to note here that the Arylarsonates are not only specific for Syphilis, but that much improvement has been found from their administration in the other conditions mentioned, notably Malaria and Yaws; also that in all these infections the causative organism is of the higher type - protozoa or spirochaetes - whether the latter belongs to the former group is still a matter for discussion; in the light of modern research some at least, including Pallidum, most probably do. (3).

We see therefore that Syphilis, although pathologically classified with the Granulomata, if not actually a Protozoal disease bears many clinical points of resemblance to that group, not the least of which is its amenability to specific therapy in the early stages - therapy by drugs which are most
 1)
 probably directly spirochaeticidal and which therefore in every sense of the word merit the term

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1. The Method of action of antisyphilitic drugs will be discussed later.

"specific".

In the course of this thesis I will give a brief outline of the history of the subject with a word or two on its present day position; thereafter the various serological tests and the comparative results of different arylarsonate and bismuth preparations will be discussed with special reference to the latter's toxicology and their effect on the Wassermann Reaction; and finally a series of cases will be appended demonstrating the practical utility of the various preparations, regarding especially serological and symptomatic improvement.

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Section 2.HISTORICAL OUTLINE.

A. The Treponema Pallidum.

The genesis of scientific Syphilology as we know it to-day was undoubtedly the discovery of the causative organism by Schaudinn in 1905, but as in all new discoveries there were forerunners to the prophet, and although naturally the flood-lights of fame envelop the latter, it is only right that we should pluck from the shadows, at least temporarily those who have preached in the wilderness.

From the very beginning the contagiousness of Syphilis was recognised and a living agent was postulated which transmitted the disease from an infected person to the normal, where it flourished and multiplied; and as far back as twenty years before Pasteur's fermentation experiments the microbiology of Syphilis was being freely discussed. The first real discovery, however, was made in 1837 by a French microscopist, Donne', who found in the primary Chancre of Syphilis certain organisms which he termed "Vibrios". By further experiments published in a "Course of Microscopy" in Paris (1844) he disproved his own theory that these were the cause of Syphilis and explained them as merely accidental. (Indeed they were probably what we know as Spirochaeta Refringens (1)). With the advent of Pasteur the microbiology of infectious disease, including Syphilis, received a stimulus

which resulted in the discovery by Lustgarten of a particular bacillus derived from primary chancres and gummata (2) - a bacillus which was received favourably at first, but was eventually discarded as merely a secondary invader. Other organisms were observed under the microscope at various intervals by many workers and advanced as the causative organism of Syphilis, but all failed to satisfy the scientific world, while cultural methods proved equally sterile of results.

Among these failures it may be worth while to mention that of Siegel because of the enthusiasm with which it was received in Germany, resulting in a systemisation of research which eventually concluded with the discovery of the *Treponema pallidum*. Siegel examined the blood and exudations of syphilitics, staining them with azur, and eosin, and found what he described as a protozoön and termed the "Cytoryctes luis". Metchnikoff, who by this time had succeeded in transmitting the disease to monkeys, experimented with this work of Siegel and finally came to the conclusion that the "Cytoryctes" had nothing to do with the disease in question. (3).

In 1903 Bordet at the International Health Congress at Brussels described the fine Spirilla which he, along with Gengou, had isolated from primary chancres using a stain of carbol methylene and carbol gentian violet, but failing to confirm these results, and these being unsubstantiated by

Metchnikoff and Roux using "hanging drop" preparations, they finally relinquished their claim and research remained in *statu quo*. Now this *Spirillum* of Bordet and Gengou was undoubtedly the *Treponema pallidum*, but it appeared that each of these workers was to play the part of Tantalus in syphilitic research, inasmuch as they just failed to grasp the significance of both their microscopical and serological discoveries.

As we have noted above, the work of Siegel was received with great enthusiasm in Germany and to confirm it a commission of experts was assembled, led by Schaudinn and Hoffmann. These soon demonstrated that the "Cytoryetes luis" was no organism at all, but only organic debris, but while doing so Schaudinn remarked a fine *Spirillum* in "hanging drop" preparations and differentiated it from the *Sp. Refringens*, which had caused confusion with other workers. (4). He gave this organism the name of "Spirochaete Pallida" owing to its slight affinity for stains of the Giemsa type. He and Hoffmann continued their work finding the *Sp. pallida* (*Tr. pallid.*) not only in primary sores but also in the glandular and epidermal lesions of the secondary stage, while the whole evidence was reinforced by Metchnikoff's demonstration of the organism in lesions of his syphilitic monkeys. To clinch the argument Buschke and Fischer (5). discovered the same Spirochaete in the spleen of a congenital syphilitic

and Levaditi (5) in a pemphigoid lesion. Thus was one of the most important microbiological discoveries practically proven to the hilt, and as time went on and technique improved more and more, investigators reported the presence of Schaudinn's *Sp. pallida* in gummata and tertiary lesions generally, and also in hereditary syphilis.

Further research lay in the study of the cellular reactions to infection and in attempts to cultivate the organism artificially. The former would form matter for a lengthy discourse in itself and cannot be discussed here, but the latter will bear passing mention. It was soon seen that this was no easy matter and presented difficulties which to this day have not been completely solved. To Volpino and Fontana (6). apparently must go the honours of first noting the multiplication of *Spirochaetes* in incubated chancrous and gummatous tissue, while later Schereschewsky (6). succeeded in cultivating them by implanting infected tissue in horse serum, but only in mixed cultures with other bacteria; Mühlens, although he obtained pure cultures of an organism morphologically ^{identical} with the *Sp. pallida* (*Tr. pallidum*), found that they were not pathogenic to experimental animals (7). It is, therefore, the name of Noguchi which is definitely associated with this research. He cultivated the organism directly from human lesions, using a medium of two parts agar, and one part ascitic fluid to which a piece of fresh sterile tissue was added

(e.g. a rabbit's kidney), the whole being topped with a layer of liquid paraffin and thus incubated anaerobically; purification was effected in sub-cultures, spirochaetes tending to grow out into the medium while other organisms remain around the needle track (in a stab-culture) (7). Considerable discussion took place as to whether these cultures were genuine, Levaditi being unable to inoculate experimental animals with the disease, but Noguchi explained this on the grounds that the strain which he had forwarded had become modified in transit, and he himself was able to inoculate monkeys and rabbits. This is supported by other investigators notably Bruchner and Galasesco and Hoffmann and Tomaszewski (8). Argument is still rife on the subject and Browning and Mackie (9) admit that "Cultures obtained have usually been without pathogenic action", while Stokes (10), quoting Kast and Kolmer, states that "..... relatively few investigators have fully demonstrated the identity of their cultured organism with the cause of Syphilis"; and further that "..... while it is possible that the virulent organism has been recovered under cultural conditions the whole problem is still unsolved". Thus the third law of Koch with regard to Syphilis remains to-day still unestablished.

In conclusion let me say a few words on that bewildering and vacillating argument, the nomenclature and classification of the organism. As we noted above Schaudinn himself called it the

Spirochaete pallida - a primary mistake as the genus intended was that of "*Spirochaeta*" in Ehrenberg's (1834) classification of spiral organisms, modified later by Cohn (1875) (11). The classification in this genus was repudiated on morphological grounds (12), and the ranks of the *Spirilla* were also closed as they were by definition "rigid" organisms. The name "*Spironema*" proposed by Vuillemin in 1905 received support from C. Dobell who justifies it in the teeth of Schaudinn's changed nomenclature of *Treponema* four months later (12). Vuillemin's suggestion was based on the assumption that the organism belonged to the Protozoa, whereas "*Spirochaeta*" was a bacterial genus (Schizophyta) i.e. belonged to the vegetable kingdom; but Schaudinn (himself a pioneer of the Protozoon theory) found that "*Spironema*" had already been applied to a Protozoon by Klebs (1892); hence his alteration repudiated by Dobell who, convinced that the organism was of the Schizophyta argued that the zoological and botanical laws of nomenclature were independent. Previous to this Noguchi had drawn up a classification of *Spirochaetes* in which he reserves the generic name "*Spirochaeta*" for a group of non-pathogenic organisms which do not swim but affect a "creeping movement" and the names "*Spironema*" and *Treponema*" for a genus whose members "differ in degree not quality", both exhibiting serpentine, twisting, and sometimes undulant movements. He applied the name "*Spironema*" to the

thicker and more energetic group (Type - Sp. recurrentis) and the name "Treponema" to their more slender brethren (Type - *Treponema pallidum*) (13). The name *Treponema pallidum* has been retained by the Society of American Bacteriologists - despite Dobell's protests - in their recent classification which divides the "Spirochaetales" into two main genera, the *Treponema* and the *Leptospira*, the former showing undulating movement and close regular spirals. This society has also designated the Spirochaetales to the order of the Schizomycetes (i.e. to the plant kingdom) (14).; but in this connection it may be noted that many workers retain the protozoon theory of *Treponema pallidum*, originally advanced by Schaudinn himself. With this regard Levaditi, Warthin, and Oslen have recently brought forward evidence of a fine granular stage in the life history, and Salesby and Greenbaum have observed this state being phagocytised by Mononuclear Lymphocytes; ring forms have also been described. Should these different forms be proven it would suggest that the *Treponema pallidum* underwent some sort of life-cycle and would argue for its protozoon origin. (15). It must be admitted, however, that the evidence is very slender, but if it were substantiated the theory would explain many of the clinical phenomena of Syphilis, including the latency of the disease and its resistance to treatment in many of its stages.

B. The Wassermann Test.

An attempt to describe in anything like fulness the discovery and consequent evolution of the various serological tests for Syphilis, with all their ramifications and differences in technique, would be quite impractical here; never-the-less mention may be made regarding the salient points in the discovery and history of the most important of these, the Wassermann Reaction, which despite the introduction of newer methods has borne the test of time and is the most universally utilised and respected of all, even to-day.

In the first place a word concerning its theoretical foundation (1) :-

If we inject any antigen into an animal, e.g. foreign red blood corpuscles or bacteria, we produce in the serum of the animal antibodies which, in the presence of complement (normally present in serum) will cause lysis of that antigen in vitro; thus a suspension of sheeps' red blood cells in saline becomes haemolysed on the addition of fresh rabbits' anti-sheep-serum;

R.B.C.'s + Serum⁽ⁱ⁾
= Haemolysis

(i)
Antibodies + Complement

but if the serum is first heated to 55°C. complement is destroyed and no haemolysis occurs. On the

addition of fresh complement, however, (for example in the form of guinea pig's serum) the reaction occurs as before.

$$\begin{array}{ccc} & & (i) \\ \text{R.B.C.'s} & + & \text{Serum (heated)} \\ & & = \text{no Haemolysis} \end{array}$$

$$\begin{array}{ccc} & & (ii) \\ & & \text{Antibodies} - \text{Complement} \\ \text{R.B.C.'s} & + & \text{Serum (heated)} + \text{Complement} = \\ & & \text{Haemolysis.} \end{array}$$

We find, therefore, that complement is thermolabile and non-specific, while on the other hand the antibody known as the Amboceptor is thermostatic and specific for its antigen. It will be seen from this that if we mix say a suspension of sheeps' cells and heated rabbits' antishoop-serum, we have an indicator for the presence of complement in another system - which brings us to the Bordet-Gengou phenomenon of fixation of complement ¹⁾ excellently summarised by Harrison (2). thus - If an animal be immunised against a given bacterium (antigen) and the heated blood serum (containing Amboceptor which is specific to that antigen), the antigen, and any fresh serum (complement) be mixed together in suitable proportions and incubated at 37°C. for say half an hour, and if then the mixture be tested for the

1. Bordet and Gengou originally used a suspension of B. Pestis.

presence of complement, none will be found, viz. complement is said to be fixed or deviated and by this process an anti-body in a given serum can be tested for, remembering that an anti-body is specific to its antigen. Such a test can be applied to bacterial disease e.g. Gonorrhoea, and it is on the basis of these phenomena that Wassermann founded his test for Syphilis. He and his associate Bruck (1905) (3) found that the bodies of bacteria were not necessary for an antigen, but that extracts of these were equally efficacious, and as cultures of *Treponema pallidum* were not available a watery extract of the liver of a syphilitic infant was used instead. The results when testing the serum of syphilitic monkeys justified their theories; a mixture of syphilitic serum, extract of syphilitic liver, and fresh normal serum when incubated in suitable quantities was found to fix complement as tested with sensitised red cells i.e. no haemolysis occurred. Human Serum soon took the place of monkeys' and again results were so encouraging when checked with clinical data that the Wassermann-Neisser-Bruck reaction became a standard test in the diagnosis of Syphilis. So far the test was considered to be a true antigen - antibody reaction, the antibodies being produced specifically against the *Treponema pallidum* in the serum of the patient, but Weygrandt (4). and others showed that watery extracts of normal liver also acted as "antigen" although not so efficiently, while later still it was shown by Landsteiner. Müller and Potzl (5). and by

Levaditi and Yamanouchi (5). that alcoholic extracts of normal organs served equally well as an "antigen" in the test as the original syphilitic infant's liver. It is obvious then, that whatever it is in the syphilitic serum which, with the "antigen", fixes complement, it cannot be true antibody to the *Treponema pallidum*; the question is one which has called forth much discussion and will be mentioned again in a later section; it has not yet been settled, but for practical purposes the test carried out with the false "antigen" is specific for the *Treponema pallidum*.

An important technical advance was made by Sachs (6). when he found that the addition of 1% Cholestrin to the alcoholic extract caused an increased fixation of complement and therefore an increased sensitivity for the test. This advance followed on the discovery by Browning, Cruickshank, and Mackenzie (7) that a mixture of Lecithin (extracted pure from ox liver) and Cholestrin acted as a potent "antigen" but this artificial "antigen" has been supplanted by the more sensitive cholestrinised alcoholic tissue extracts. Many other lipoids and allied substances capable of antigenic properties were tried out, but none of them have proved satisfactory, and they have more or less fallen out of use, the crude extracts being apparently more potent. Of all the artificial preparations Harrison considers that the ox-liver - lecithin and cholestrin of Browning and Mackenzie

is the most reliable and Noguchi has devised a similar extraction. (8).

The further story of the Wassermann Reaction became to a greater or lesser extent a matter of individual preference in technique and in the use of the different sensitised haemolytic systems and various antigens, until to-day it has been said that there are as many techniques as there are laboratories which perform them. Stokes (9) gives the comparative table of the various tests, drawn up by the Second Serological Conference of the League of Nations at Copenhagen in 1928, and according to these results the method employed by the British Ministry of Health (Medical Research Council No.1) and that advocated by Harrison ranks first of the complement fixation tests as regards specificity. A somewhat fuller account of this method will be given in a later section, but it may be mentioned here that a single antigen is used, namely, a sensitised sheep's cell haemolytic system. Browning and Mackenzie (10). advise the additional use of a Cholestrinised liver-lecithin antigen in a check system, especially when the reaction is being tested for the control of treatment, and Stokes also considers the use of a duplicate antigen advisable, although he deplores the use of multiple antigens still employed by a few workers(11).

As regards the Nervous System, Wassermann and Plaut (12). were the first to apply the

Wassermann Reaction to the Cerebro-Spinal Fluid in General Paralytics and their number of positive reactions substantiated the hypothesis that Syphilis was the causative factor, an hypothesis which was proven later by the demonstration of the Treponema pallidum in the Cerebral cortex and Cerebro-Spinal Fluid. Similar positive results were found in Tabes Dorsalis (although not so constantly) and in Meningo-Vascular Syphilis.

It will be seen from this resumé of its history, brief though it be, that the Wassermann Reaction has proven its worth more by a process of trial and error than on the rock-like foundation of scientific rationalism; never-the-less it has been, and still is a veritable spur in the flanks of syphilologist, serologist, and general physician alike, and has lightened our darkness in the investigation not only of the individual case, but of the whole gamut of syphilitic diagnosis and therapy.

*Luminous
spur!*

C. The Arylarsonates and Bismuth.

Although we fully embrace the sentiment that medicine is an art and never will be a true science, we submit that most of its professors would gladly forego in part the title of "artist", could they but see a little more of the Truth, bubbling

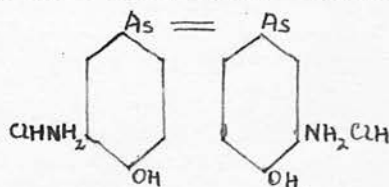
forth from its proverbial well - a Truth, which, if confined to the realms of science in its popular sense, must be based and reared on reason. It is then with pleasure, nay enthusiasm, that we turn to Ehrlich's production of Salvarsan, one of the few achievements that mitigate our fardel of empiricism in therapeutic medicine, blazing as it does an objective trail amidst a pathless jungle of vague facts and fancies.

To the consummation of Salvarsan there were many contributors, but the genealogical tree may be said to have commenced with the production of "Trypan Red", a dye of the Benzo-purin group, to which "Sulpho-" groups had been introduced, and which had been proven to have definite trypanocidal properties. The addition of arsenic to the molecule resulted in the marketable product "Atoxyl" (the sodium salt of p-arsanilic acid), the work of Béchamp (1863) (1) and later of Landsberger and Blumenthal (1). It was the action of this drug in Trypanosomiasis and experimentally in the Spirotrichosis of hens which led Ehrlich to consider its possibilities in Syphilis, and for some time it was used in conjunction with mercury in the therapy of that disease. Beddoes summarises its beneficial effects thus; "It is especially indicated when the beneficial effect of mercury is temporarily exhausted and when there is mercurial stomatitis. It causes a recovery of health and strength, renders the system better able to tolerate mercury and it is

especially indicated when the results of mercury and iodides do not come up to expectation Except when patients can be kept under close observation arsenic treatment must at once be followed by mercury" (2).

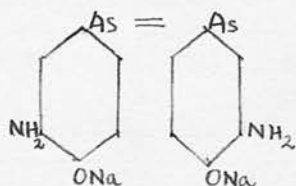
Not only were these therapeutic claims for Atoxyl very humble, but the drug was found to have definitely toxic effects, the most important and frequent of which was the production of optic atrophy; and as a result of this Atoxyl fell into disuse. But such a reverse merely stimulated the genius of a man of Ehrich's calibre. He was not long in synthesising a substance "Arsacetin" by the introduction of an acetyl molecule into the amino group of arsanilic acid, thus decreasing the toxicity of the latter three to ten times; and by his observation that Atoxyl and Arsacetin, although in small amounts capable of destroying trypanosomes in vivo could not do so in concentrations of 25% in vitro, he postulated the theory that these pentavalent arsenic compounds were reduced in the body to trivalency, when they exerted a greater trypanocidal effect. (3). His hypothesis was verified experimentally by the production of diamino-arsenobenzene - a trivalent derivative of arsanilic acid. He also recognised the trypanocidal effect of introducing the amino (N.H_2) and hydroxyl (OH) radicals into the arsenobenzol molecule in ortho position to each other and later the important role which a Cl group plays in the therapeutic specificity for Syphilis (3).

Without going into the too intimate chemistry of the subject he succeeded on the basis of these findings in introducing Dioxydiamido-arsenobenzol di-hydrochloride (Salvarsan) - the result of his 606th. experiment and therefore known as "606".



Dioxydiamido-arsenobenzol di-hydrochloride

This elaboration was tried out experimentally in animals by Hata who found that in its original acid solution it was most irritating and most toxic and advised, with Ehrich's agreement, that it should be administered after alkalisation to the disodium salt (4).



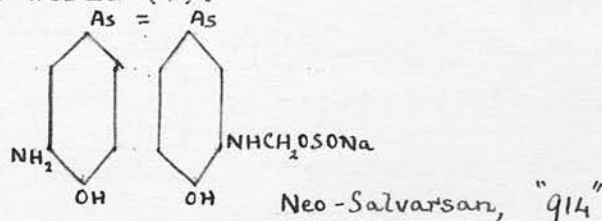
Di-sodium salt of Dioxydiamido-arsenobenzol.

Finally, after passing through an elaborate experimental stage carried out by workers all over the world it was placed on the market as Salvarsan in December 1910 (5).

The enthusiasm with which it was received by the profession knew no bounds and the idea of "Therapia sterilans magna" was so intoxicating that one wonders how Salvarsan ever survived the natural reaction, when Erlich's dream of sterilisation in a single dose was shattered, on the report in due course of relapses and recurrences after the first happy

disappearance of symptoms. Despite these disappointments and its present supercedence by more applicable derivatives Salvarsan remains " - - - a triumph of constructive thinking that within one decade raised empirical medicine and rule of thumb syphiology - - - to the dignity of an exact science" (6).

Not content with this remarkable elaboration, Ehrlich continued his investigation on the subject with a view to eliminating (1) the toxicity of the drug which had come to light with its general use, and (2) the complicated technique of the administration. As a result of these investigations he produced at his 914th. experiment "Neo-salvarsan", a condensation product of Formaldehyde-sulphoxylate of soda and dioxydiamido-arsenobenzol, which had the advantage of being freely soluble in water and being neutral in reaction and hence could be administered with a 20 cc. syringe without alkalisation - an advance which has made syphilitic therapy a practical proposition to every general practitioner throughout the world (7).



More recent development of these two groups of drugs has aimed at (1) a combination with the heavy metals to increase their spirochaeticidal effect and (2) the discovery of derivatives which would be less painful on intramuscular injection as both the

original "606" and "914" products cause necrosis and sloughing when administered in this way. A more detailed account of these derivatives will be given in section 4. (N.B. the "606" group of drugs was originally under the control of German patents, and it was only during the Great War that they became manufactured by other Nations with the adoption of their own terminology e.g. Kharsivan, arsphenamine, arsenobenzol, etc.; with the advent of the "914" group the prefix neo- or nova- was attached e.g. Neo-kharsivan, neo-arsphenamine, novarsenobenzol).

A word concerning "Tryparsamide" (Sodium salt of N-phenyl-glycine-amido-p-arsonic acid), a relative of Atoxyl and therefore a pentavalent arsenical. This drug was evolved by Jacobs & Heidelberger of the Rockefeller Institute in 1917 (8) and first used in man by Pearce (1921) (9) with striking results which stimulated Losinsz and Loevenhart (8). to administer it in cases of neurosyphilis (1923). Since its discovery it has been under the strict supervision of the Rockefeller Institute, which has rather restricted its popularity - wisely perhaps in view of its occasionally producing optic atrophy; moreover as Stokes points out its efficiency was somewhat overshadowed by malarial therapy "introduced with the Viennese seal & ribbon" (8); so that, what with one thing and another, it is small wonder that the profession is only now beginning to realise the hopeful future it prophecies for the tabetic and paretic.

As Jonathan to David, so is Bismuth to the Arylarsonates in our present conception of the orthodox treatment of Syphilis; hand in hand for the past decade have they led the van in our war against the disease, gaining in popularity and efficiency and becoming more closely associated with every succeeding victory.

Balzer (10) in 1889 was the first to comprehend the possibility of Bismuth in Syphilis, but his experiments on dogs using the ammoniacal citrate were thoroughly disappointing as this salt is probably one of the most toxic of all the bismuth compounds especially in regard to the nerve centres and gastro-intestinal tract. It was not, therefore, until 1916 that experimental work was resumed by Sauton and Robert (11) who used sodium tartro-bismuthate in hen spirillosis with excellent results. Following Sauton's tragic death in the War his studies were continued by Sazerac and Levaditi (1921) (11), employing the same compound in the Syphilis of rabbits with such encouraging effects that they were led the following year to employ it in man, and concluded that Bismuth ranks higher in effectiveness than Mercury and only slightly inferior to the Arsenobenzol compounds - a statement established by Fournier and Guenot (11) and later by clinicians throughout the world, until Mercury was in danger of being completely eclipsed. Contemporary argument rages around the respective merits of metallic bismuth and insoluble and soluble compounds, while

more recently fat-soluble preparations have gained something of a reputation as being more rapidly curative. Compounds of Bismuth and Arsenic have scarcely emanated from the chrysalis of experiment but have so far proven very satisfactory; in this connection it is interesting to note that Levaditi and Fournier (12) championed the effect of Bismuth - Stovarsol by mouth - a revolution in therapy as far, at least, as the bismuth is concerned.

I have tried in these pages to give some idea of how the three main salients have been established in our front against Syphilis; they are not impregnable; many reinforcements are required before they can make any decided advance into the enemy lines; but up to date they have borne the brunt of the battle and are monuments to the genius of those who have conceived them, infusing new and inspiring blood into the veins of a whole army of satellites.

Section 2.References:

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Section 3.SEROLOGICAL DIAGNOSIS AND ITS VALUE.

The secondary place to which all writers relegate laboratory methods in the diagnosis of Syphilis is a theme which they never tire of emphasising, lauding clinical observation and acumen in the individual case above any stereotyped impersonal examination of body tissues and fluids; but, alas, a few days introduction to many venereal clinics materialises these ideals in practice into a dark-ground examination of the primary sore, a two years course of injections with intermittent serological and cerebro-spinal fluid examinations, and further observation and treatment based on the findings of the apparently omniscient serologist. In short, the laboratory and its methods are in great danger of becoming the masters instead of the servants of the venereal clinician, despite the italics and heavy type of the literature. Now this sorry state of affairs (and I think that most of those with experience will agree that it exists) is due to three factors:- a. The mass production of the clinic system, where time is a consideration of the first magnitude which can only be attacked by the development of a strict routine and the elimination of that extra personal attention which means so much in the treatment of any disease - the "**Ars in rebus medicis**". b. The natural inclination of humanity to tread the path of least resistance - and medical men are by no means immune. c. That

childlike all embracing faith with which many clinicians view a laboratory report, a faith comparable only to that which is imbued in the patient for the former's "bottle". As a result of this servility the Syphilologist is rapidly being reputed by the profession to be a man merely of syringes and test tubes, microscopes and slides, "cure-tests" and reports, whereas in reality there is no man who requires a wider clinical knowledge, whose judgment is more critical, whose intuition should be more sensitive, and whose acquaintance with other branches of medicine should be more catholic. Know Syphilis, says Osler and everything else will be added unto you; the corollary is obvious and equally true - To know Syphilis everything else must be added unto you.

But let me not be misunderstood in this - I have no wish to disparage the true value and significance of the Wassermann Test and its allies; the chief engineer on board ship is a most important and indispensable member of the ship's company, but his place is the engine-room, and to transfer him to the bridge would result not only in navigational chaos, but in a completely erroneous and unfair estimation of the man's competence. So with the serological tests- they have a commanding position in Syphilology, but they are not the Alpha and Omega, and any attempt to make them so is both derogatory to them and an impediment to the full

and just consideration of the whole problem.

Theory of the Serological Tests.

The multiple serological tests for Syphilis are, in the main, variations in technique of the two principal groups - the complement-fixation and precipitation reactions; but before entering into any discussion of the significance and comparative value of these it is necessary that we understand fully their immunological basis.

When we inject bacteria into an individual, (as we saw in section 2), or what amounts to the same thing, when an individual is infected naturally by an organism, there are produced in that individual's serum various antibodies, possessing reacting properties with the antigen, which are demonstrable in vitro. These antibodies are of several different types, but those demanding our attention at present, as being probably the prime factors in the syphilological reaction, are two in number - the immune body or amboceptors, and the precipitins, the former causing a fixation of complement and the latter a precipitation or flocculation of the antigen.¹⁾

Now as a general rule an antibody is formed which is specific for its antigen and will react with no other (and conversely), but this is not absolute and it is this exceptional non-specificity,

1. Immune bodies and precipitins are closely allied and are probably different reacting properties of the same antibody. (1)

or rather qualified specificity, of antigens both with regard to their production of, and their reaction with antibodies that interest us here. It has been shown by Landsteiner for instance, that proteins combined with various substances of known constitution (e.g. organic acids) and used as antigens, will produce in an individual's serum antibodies which have an immunological affinity for these substances (organic acids) in vitro, although the latter by themselves will not produce them in the serum. In other words it is the protein which stimulates the formation of the antibody but the additional substance which qualifies its specificity (2). Again Forssmann has demonstrated that by an injection into a rabbit of guinea-pig's emulsified tissue we can produce an haemolysin (immune body) to sheep's red blood corpuscles. This haemolysin (Heterophil antibody) along with lipoids extracted from the guinea pigs' tissue with alcohol (Heterogenetic antigen) causes fixation of complement in vitro, although the lipoid will not develop such an antibody when injected itself; the addition of foreign serum, however, restores its antigenic properties, and so it would appear that in this case there is some substance in normal serum (and tissues) which promotes the antibody formation while the lipoids qualify it (3); or according to Browning & Mackenzie (4) "It would appear that the power of producing such lipoidophile antibody resides in some lipoid-protein complex, whereas combining affinity rests with the lipoid." These

immunological effects of lipoids should be borne in mind while we are discussing in the following paragraphs the Wassermann and Precipitation Tests, both of which most probably depend on the same principle.

A statement as to what we really know of the Wassermann Reaction must of necessity be brief and can be summarised thus - Certain tissues rich in lipoids (cholestrin etc.) have the power when mixed with syphilitic serum of inactivating complement; the reaction is most constant in Syphilis, but occurs also in various other diseases. The Theories to explain this phenomenon are manifold and monuments of ingenuity which yet form but a thin veneer to the plain wood of complete ignorance.

Schmidt, a strong supporter of the physico-chemical basis, demonstrated that the particles of the "Antigen" emulsion were electro-negative and put forward the theory that these might be neutralised by positively charged globulin, resulting in colloidal precipitation of the particles, whose free surfaces would then adsorb complement. The Albumen of normal serum prevented this reaction, but in the syphilitic for some unknown reason it was unable to do so (5). Sachs, also working on the view that the reacting property of positive sera is due to an alteration in the globulin, believed that the globulin of syphilitic fluid was more easily precipitated in the presence of tissue extracts because of a difference in its dispersion; the

precipitin then adsorbed complement (5).

Following on the observations of Kendrick & Kahn, who found that the syphilitic "antibody" was carried down in the globulin when syphilitic serum was treated with 50% ammonium sulphate (6), there seems little doubt that the said antibody is definitely associated with the latter factor. Again it has been demonstrated by Sachs & Georgi that the formation of a precipitate in positive sera is closely connected with the fixing of complement and these workers agree that the two phenomena are probably complementary (5)⁽¹⁾. Kolmer while admitting the validity of this work and agreeing "that the results of precipitation produce such changes in the physical chemistry of the fluids that complement is inactivated and that this constitutes what is designated as complement fixation", denies that the deviation of complement is adequately explained on an adsorption basis and suggests rather that the changes in the colloidal conditions of the fluid *per se* is the causative factor. (8). So much then for the most important of the physico-chemical theories - they have made somewhat unsatisfactory attempt to explain the mechanism of the phenomenon and no attempt whatsoever to explain its underlying cause, other than the assumption of

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1. Mackie has recently disagreed with the hypothesis and has separated two constituents from the serum each being responsible for its particular reaction; Mackie states that these are inhibitory to one another (7).

a pathological accident. In this connection also it may be added that attempts in vitro to confer a positive state on negatively reacting sera by the addition of various substances such as insulin, staphylococci cultures etc. have not proved fruitful of results; the few successful attempts have shown that the alteration is purely temporary and unable to resist heating to 55° C. (9). One thing these physico-chemical investigations have brought to light, however, is the fact that the syphilitic antibody is closely associated with the globulin of the serum, thus agreeing with experimental evidence of antibodies in general, and suggesting that those of Syphilis conform to the general rule.

Let us turn then to explanations based strictly on an immunological conception of the test which have gained renewed credence with the verification of Forssmann's experiments described above. The "Auto-antibody formation" theory suggested by Weil and Braun (10). postulated the production of toxic substances of a lipo-protein nature from the individual's tissue cells during the course of the disease. These lipo-protein complexes stimulated antibodies which were antagonistic to themselves and which therefore reacted in vitro with the lipoidal portion of the complex as contained in normal tissue or alcoholic extracts thereof.

According to Citron's views a syphilitic toxin united with the lipid in the body, and this union acted as antigen to the production of antibodies

which fixed complement and formed a precipitate when mixed in vitro with the lipoid itself i.e. alcoholic extract of tissue cells (10). Now these theories although formed not long after the discovery of the Wassermann Reaction itself, have not only been strengthened by modern research, but actually b'ring the serological tests for Syphilis into line with what we know of general immunological principles; and indeed it seems somewhat illogical to explain on any other grounds a phenomenon which is identical, as far as visual evidence goes, with phenomena of other diseases where we are quite satisfied with an antigen-antibody explanation. But in passing might it not be possible to incorporate Weil and Braunn's, and Citron's views together with Forssmann's experiments into a rather different hypothesis?. Might not the degenerating protoplasm of the *Treponema pallidum* form a lipo-protein similar to that present in tissue cells, which would stimulate the formation of antibodies naturally selective for tissue lipoids in vitro? Might not all degenerating protoplasm of the higher infective organisms form a similar antigen and thus explain the occurrence of a positive Wassermann Reaction in Yaws, Malaria, Trypanosomiasis, Relapsing Fever, etc.? Is it not possible that the protoplasm of the cells of the body undergoing toxic or degenerating changes might not stimulate the formation of antibodies by an analagous

antigenic process of their waste products and consequently explain the positive Wassermann Reaction in such widely different conditions as Pernicious Anaemia, Chloroform poisoning, high pyrexia of any origin, the serum of the cadaver, etc.? and in this last connection it is interesting to note that the protoplasmic changes of fatty degeneration and cloudy swelling are of a molecular nature not unassociated with lipoids according to modern morbid histological investigation. Again, have we not in this theory an explanation of the therapeutic benefit of Malaria in general paralysis of the insane? These suggestions I hasten to admit are purely personal and are therefore advanced with a becoming humility and with no attempt to dogmatise, but rather to indicate fairly logical, if hypothetical conclusions, on the admitted facts and experiments; I can find no suggestion of them in the literature either for or against; that there are objections to them I fully agree, not the least of which is the comparative rarity of the Wassermann Reaction as recorded in other conditions than Syphilis, but until we know more about immunity in general and the Wassermann Reaction in particular I do not see how they can be utterly confounded.

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Clinical application of the serological tests.

The reputation of any scientific test applied to medicine must in the end be judged by its general agreement with clinical findings, and it is on this standard that we must estimate the utility of the serological tests in Syphilis; leaving out of the question for the present all reference to faulty laboratory technique (perhaps a more frequent factor than is generally admitted), we may form conclusions of the true worth of these reactions by a discussion under the following headings:-

1. The positive reaction in non-Syphilitics.
2. The negative reaction in Syphilitics.
3. The true positive reaction and its significance.
4. The effect of time and treatment on the reaction.
5. The reaction in the Cerebro-spinal fluid.

(1) The positive reaction in non-Syphilitics.

Upon this rock many a proud immunological theory has foundered, but for practical purposes the channel is quite navigable when a pilot of clinical common-sense is taken aboard. Our first consideration must be, that often it is quite impossible, short of microscopic sections of every body tissue, to definitely state whether a positive reaction is false, and it is very probable that many of the cases of disease giving so called false positives are merely conditions superimposed upon

a latent syphilis; but nevertheless false positives are so frequent that most Syphilologists are unwilling to brand a man with the stigma of Syphilis or to enrol him on a long and hazardous course of treatment on the evidence of one Wassermann Reaction, however strongly positive it may be; and Stokes even goes so far as to say that he has "gradually come to recognise that the single positive Wassermann Test that is unaccompanied by any other detectable evidence of the disease - - - is likely to be a false or nonspecific positive(11)."

As regards the actual diseases in which the Wassermann Reaction has been recorded I quote a list from Stokes' Clinical Syphilology (Fig. 59). Now although this list is numerically impressive a little consideration shows us that a great many can be ruled out on purely clinical grounds, and that most of the remainder have such a geographical distribution that they fail to enter into a practical differential diagnosis in these temperate zones. The really difficult cases are those with Tuberculous skin lesions, which often bear a striking resemblance to Syphilides; moreover as they often react favourably to anti-syphilitic treatment the diagnosis is not at all helped by the "Therapeutic Test". Confusion in this regard, however, is the exception rather than the rule, and even in these exceptions careful observation will soon establish the diagnosis beyond question.

A Classification of the Occurrence of Biologically False Positive Serological Reactions for Syphilis

Frequent or Undoubted	Occasional	Disputed
Yaws	Ulcus Molle with Buboës	T. B. various types especially glandular
Recurrent Fever	Lupus Erythematosus	Malignant Tumours
Trypanosomiasis	Leukaemias	Psoriasis
Spotted Fever	Pernicious Anaemia	Pemphigus
Leprosy	Certain skin Tuberculosis particularly Papulo-necrotic	Apthae
Scarlet Fever	- Tuberculids	Basecslow's Disease
Tropical Sore	Serum obtained under Anaesthesia	Plumbism
Endocarditis and Septicaemia	Serum obtained after Death	Diabetes
Malaria		Eclampsia
		Leishmaniasis
		Pellagra
		Beri-beri
		Pregnancy

In considering this list it must be remembered that it has been compiled on the results of all techniques, and that a far greater specificity has been claimed for the more modern methods. Indeed Kolmer declares that with his procedure the true non-specific positives occur, only in Yaws and occasionally in Relapsing Fever (12). The precipitation tests are said to be even more specific than the complement fixation methods (13). As regards actual statistics, these vary enormously for given techniques relative to various individual diseases, and if, according to Browning & Mackenzie, we look upon the change occurring in positive sera as quantitative rather than qualitative (and there is apparently no doubt of this) it is obvious that too sensitive a method will undermine the specificity thereof. They consider that over delicacy of a procedure is a defect as far as diagnosis per se is concerned, and advise the reservation of such techniques for the estimation of therapeutic improvement. With this preliminary criticism they fully review the literature on the false positive and consider its frequency to be in the region of 1 in 100 and 1 in 1000 cases of non-syphilitics, these positives including especially Yaws, Malaria, and Trypanosomiasis. They emphasise the possibility of an underlying syphilis in many of them, and point out that in very few was the Wasserman Reaction strongly positive with modern methods. (14).

To sum up this part of our discussion we may say that it behoves the Physician to use the test as an adjunct to his clinical judgment, and that although a positive reaction is strong evidence in favour of Syphilis one should have it repeated after a due interval, and in addition remember that Syphilis does not confer an immunity on the individual for other diseases and that the lesions in question may have an aetiology quite dissociated from the Trep. Pallid. despite the results of Serological examination.

2. The Negative Reaction in true Syphilis.

A negative reaction of the serum to the serological tests means exactly nothing, either in relation to diagnosis or prognosis, and as far as the former is concerned a weakly positive serum closely approximates to this unsatisfactory conclusion - a fact even admitted by Kolmer on his personal modification of the Wassermann Reaction, when he pleads for the repetition of the test at least, in the event of such an indeterminate result (15).

A lack of appreciation of this among general Physicians rather than Syphilologists, has lead to a depreciation of the true value of the Wassermann Reaction. The Physician appeals to the serological oracle; to his mind, it perchance prophecies falsely; therefore nothing but treachery can emanate from it! An irrational judgment which human nature is too ready to embrace.

A negative reaction of the serum is the rule rather than the exception until late in the primary stage, and it is usually just prior to the appearance of the secondary epidermal and glandular manifestations that the blood acquires its positively reacting properties (only exceptionally has a positive been recorded before the appearance of the primary sore) (16). Thereafter throughout the secondary stage a negative blood is practically unknown, and it is only later in the latent or tertiary periods of the disease that negatives become increasingly more common, varying in their numerical ratio to positives, according to the nature and site of the pathological lesion and the type of test used. As regards the sensitivity of the various procedures in different stages of the disease, no consensus of opinion appears to be available among different investigators, and although the Kahn Test (Precipitation Test) (17). appears to rank high in the opinion of many (not the least of whom is its originator), and in the comparisons of the League of Nations Serological Conference (1928), many authorities favour the newer complement fixation methods. Stokes, after quoting contradictory experimental evidence of Greenbaum, Becker, Houghton and others concluded that one technique at least of both the complement fixation and precipitation tests should be employed in the interpretation of a negative serum. (18).

In congenital Syphilis negative results are much more frequent even in the presence of active lesions; this is emphasised by Fischl and Steinert (19). while Browning and Mackenzie recorded a series of fifty four cases of active congenital Syphilis at various ages in which fourteen were serologically negative - this, as a refutation of Boas' assertion that the Wassermann Reaction is more pronounced in congenital Syphilis than in any other form (20). Kolmer points out that many syphilitic children who react negatively immediately after birth develop positive sera two or three months later, and he also considers that the incidence of negatives in children showing active manifestations at birth is practically infinitesimal; in passing he remarks that many women who are positive during pregnancy become negative in the puerperium, but offers no explanation(21). Similar results are reported by Kahn with his precipitation test (22).

Among those conditions which may inhibit a positive serum, alcohol is the only drug which may, according to some investigators, have this effect. Craig and Nichols, and Boas all champion this observation and record intervals varying from several hours to two or three days during which the inhibitory action may last (23).; but all authorities do not agree either to the duration or alterative effect of the drug, while Lees mentions it as a caution when taking blood for the test (24).

Hyperpyrexia is also said to occasionally abolish a positive Wassermann Reaction for a short time. (23)

The reactivation of a negative Wassermann by a provocative injection of one of the Arsenobenzols (or Bismuth compounds also) a few days before taking a specimen was first noticed by Gennerich as early as 1910 (25), but no valid explanation of the phenomenon has yet been offered, although Browning and Mackenzie consider it as a variation of the Jarisch-Herxheimer Reaction and attribute it either to a stimulation of the Treponemata or a liberation of endotoxins following on their destruction (26). Clinically its uses lie in reinforcing a weak positive for purposes of diagnosis or in an estimation of the thoroughness of treatment.

3. The True positive Reaction and its significance

In the primary stage of Syphilis the Wassermann Reaction must take second place as a diagnostic procedure to the microscopical examination of the chancrous serum or local glandular material, but in some cases these primary lesions are in a state of retrogression before the appearance of the secondary rash and we then must rely on our serological tests to confirm a clinical diagnosis; this, it might be added, is especially true in the case of pregnant women where secondary manifestations

are often fleeting and slight (27). It is, however, in the acute generalised stage of Syphilis that the examination of the blood serum reaches its maximum sensitivity, most investigators estimating the positives in these cases at approximately 100%. Thereafter with the dimming of the clinical picture and the localisation of the pathological lesion positive serum reactions become less universal varying from 50% to 80% in latent Syphilis and 80% to 96% in clinically detectable lesions of the tertiary type (excluding lesions of the central nervous system), according to the system affected. Thus lesions of the cardiovascular system adhere more closely to the lower percentage, while those of the skin more commonly accompany a positive blood (28). (These figures are based on the Kolmer- Wassermann technique; for details and comparative tables the reader is referred to Stokes' Clinical Syphilology, 1934, Figs. 65 and 66; Kolmer, Serum Diagnosis by Complement Fixation, 1929, page 493; Kahn, Diagnosis of Syphilis by Precipitation Test, 1925, Table 46).

We see, therefore, that the serological tests for Syphilis bear a fair degree of positive diagnostic assurance even in tertiary and latent stages, and as these cases, often bearing a striking resemblance to other diseases, frequently find their way to the general departments of a hospital, a routine serological examination for Syphilis in every case where a diagnosis is in

the least doubt, has been mooted by many authorities.

The danger of such a routine stultifying clinical observation is obvious, but in many surgical cases, for example rectal growth, such an expansion of the use of the Wassermann Reaction might save a patient from the ravages of an unnecessary and dangerous operation; nor can the general physician appreciate too fully the ubiquity of the *Treponema Pallidum* among "the thousand natural shocks that flesh is heir to".

The period of possible infectivity of the disease (a question which must always remain poignant to the victim with any sense of moral rectitude), receives but little elucidation from the serological tests. The problem depends more on a consideration of the duration of the Syphilis and the treatment administered. A positive reaction, however, in the first few years of infection is strongly in favour of the patient being infective, while later (ten to fifteen years after the primary sore) although the strict regime of continence might be relaxed to a certain extent, it is as well to look askance at unprotected marital intercourse and to institute some form of therapy during its resumption. No relaxation must be permitted on the evidence of negative serological tests alone (29).

4. The Effect of Time and Treatment on the Serological Tests.

After the acute generalised stage of the

and Bismuth, but the inclination to treat a laboratory report rather than a human being cannot be too strongly resisted; and while a negative Wassermann may be a legitimate goal in primary, secondary, and certain tertiary syphilitics no harm would accrue were the physician to eschew the laboratory altogether in such visceral lesions as aortic aneurysm, advanced tabes dorsalis, etc. where our main object aims not at sterilizing the patient, if that is possible in any case, but in increasing his expectation of life and in rendering his remaining years as comfortable and productive as possible.

Serological tests which remain irreversible after adequate treatment are known as "Fast" positives, and the interpretation of the phenomenon has evoked divergent opinions, one school arguing that a positive reaction indicates the presence of the organism, and the other pointing out quite reasonably that in some cases of Syphilis the infection may call forth a serological change which is permanent (at least for some years), and will create a positive Wassermann Reaction without any further stimulus. Most authorities, however, disagree with this latter view on clinical grounds and Kolmer summarises the majority's opinion when he writes that he has "had but few cases of Wassermann-Fast Syphilis in whom some evidences of infection were not found by combined clinical,

roentgenological, and laboratory study; - - - all require continued observation and periodic courses of treatment" (3). We may take it then, for practical purposes, that the positive serum means the presence of the *Treponema pallidum* in some part of the body, and that due observation and care of the case should be displayed in consequence; perhaps no case requires a more discriminating judgment in exhibiting or withholding treatment.

5. Serological Tests on the Cerebro-Spinal Fluid.

No discussion of the serological syphilitic tests would be complete without some mention of their relation to the Cerebro-Spinal Fluid and Neurosyphilis where they probably reach their zenith of specificity. Only the Wassermann Reaction will be discussed, however, as the precipitation tests (Kahn, Kline, etc.) are found either to be too complicated in their technique or else unreliable in their results. General paralysis of the Insane is the form of Syphilis which gives the highest percentage of positive fluids (91% to 98%), while in diffuse Neurosyphilis the proportion is in the region of 80%. (31). in *Tabes dorsalis*, however, a considerable fall results and Browning and Mackenzie put the figure as low as 54%, working on an analyses of 456 cases at various stages of this form of Syphilis; these workers appear to be particularly unfortunate in their collection of cases as most authorities consider the proportion

much higher and Lees estimates it at 75% to 80%. (32). It is only fair to add that the former founded their percentages on a series of cases many of which had actually been treated; they point out also that the Wassermann Reaction is more frequently positive in early Tabes than in the later stages of the disease, when the infection may apparently burn itself out, and the resultant symptomatology be due to the devastations of its previous progress (33). Moreover the newer techniques of the test such as the Kolmer modification, are much more sensitive and especially is this true when large quantities of Cerebro-spinal fluid are used (up to 1 cc). Kolmer's figures quoted below, although rather enthusiastic are probably a fair enough representation of the sensitivity of the more modern procedures (34).

	% Positives in C.N.S.
Asymptomatic	80% to 90%
Tabes Dorsalis	96%
Paresis	100%
Cerebro-spinal Syphilis	95% to 100%.

So much then for those cases of Neuro-syphilis which may be said to have earned a passport into the domains of the neurologist and psychiatrist. More interesting, because requiring more prognostic and therapeutic discrimination are those fluids which present a pathological picture in the secondary stage with no clinical evidence of involvement of



the central nervous system. About 40% to 45% of patients with fully developed secondary Syphilis present abnormalities in the Cerebro-spinal fluid analogous to those of Tabes dorsalis, Paresis, etc., but in only a few of these cases can a positive Wassermann Reaction be demonstrated. The prognostic significance of these abnormalities lies in the fact that, while in many cases they disappear with time or routine treatment or both, in a small proportion they persist, and the underlying pathological lesion which they all indicate progresses to a definite clinical entity. With this regard the Wassermann Reaction must be read in conjunction with the cytological and colloidal gold investigations, and with the globulin estimation of the fluid. (Of course this is true of all C. S. F. investigations from a syphilological standpoint, but from the view of pure prognosis as opposed to diagnosis it is especially indicated in the type of case under discussion). Stokes emphasises the advantages of a quantitative complement fixation procedure and stresses the importance of a strongly positive Wassermann associated with a first zone colloidal gold test; he considers that such a combination signifies the "Red Flag" of warning to the Syphilologist demanding early and intensive treatment with Tryparsamide and fever therapy to insure against a clinical paresis of the future (35). In this Kolmer agrees with him (36), and both these workers are of the opinion that the Wassermann Reaction

of the Cerebro-spinal fluid should be performed early in the patient's Syphilis as a routine (three to six months). Lees considers that the end of the first year is soon enough in the practical conduction of an asymptomatic case (37).

The effect of treatment with "914" compounds on a quantitative Wassermann Reaction is given in a series of cases by Fildes and Parnell (38). the amount of 914 used varied from 1 to 4.5 Gms., and the results, although not striking, yet demonstrate a definite improvement in the Wassermann Reaction of the C. S. F. by the Arylarsonates while the more modern tryparsamide and malarial therapy has even more satisfactory serological results in suitable cases. Hence the importance of early Lumbar Puncture (The subject will be discussed further in the section on treatment).

The false positive of the Cerebro-spinal fluid is more or less of academic interest only; it has been recorded in nearly all the commoner neurological diseases but is of such rarity, and in such cases where clinical symptoms are obvious that no real importance need be attached to it. The very rare occurrence of a positive Wassermann Reaction in cases of brain tumour may cause some confusion with a diagnosis of gumma, but even in these cases it is quite possible that the patient has Syphilis in addition to the Neoplasm (39).

Some technical modifications of the serological tests.

A detailed technical description of all these tests and their modifications is beyond the scope of this thesis; such a task requires the endurance of Sisyphus and the pertinacity of Hercules, and moreover would be as fruitless for our present purpose as the labours imposed upon these victims of a vengeful Olympus. What I wish to indicate, however, is some of the more important personal differences dealing with the complement fixation methods under the headings of their various reagents, and mentioning briefly the precipitation procedures later.

A. The patient's serum.

Inactivation of the patient's serum by heating to 55°C. is practically universal now among modern workers, and few use this medium alone for their source of complement. The duration of heating varies, but the average is in the region of half an hour; Harrison, however, recommends only ten minutes arguing that the longer interval decreases the reacting power of the serum, and that the anti-complementary property of normal serum is reduced sufficiently in the shorter time (40). Kolmer considers 15 minutes as sufficient; he points out also that this is not so much for the destruction of normal complement, but for the abolition of anti-complementary substances which provoke false

positives (41). The latter uses different dilutions of the serum to give quantitative readings for his modification, and in this he agrees with the method of Boas and Thomsen (42).

B. The Antigen

There can be no doubt that the type of extract used accounts for a large proportion of contradictory results, and not only this, but different methods in the preparation of the same antigen will determine different readings especially in border-zone cases. We saw in Section 2 that Sachs recommended the addition of 1% Cholestrin to whatever extract was used; and it is with this addition that Medical Research Council No. 1. on Harrison's recommendation use alcoholic extract of human heart. Thomsen and Boas found this extract uniformly satisfactory (although they advise a fresh supply every week), and Fildes and McIntosh after extensive investigations on the subject advise it before all others (43). Kolmer has evolved rather a complicated technique of preparation (extracting the tissue with ether, acetone, and twice with alcohol, and adding only .2% cholestrin) and considers that its increased accuracy warrants the extra trouble and expense; according to Kolmer it is immaterial whether one uses beef or human heart, and no check system using alternative antigens is necessary (44). The

lecthin-cholestrin mixture of Browning & Mackenzie, although possibly of value as a control is not sufficiently sensitive as a solitary test (45).

In Wassermann's laboratory the alcoholic extract of syphilitic liver is still in use, but most authorities consider that other antigens are of equal efficacy and more easily procured. Noguchi in his method used the liver, heart, or kidney of man, ox, guinea pig, rabbit, or dog, and considered all equally suitable (46).

We see, therefore, that there is a fair diversity of opinion on the comparative efficiency of the various antigenic substances, and the method of their extraction, but a rich supply of cholestrin is common to them all and is the predominating factor. Again it must be remembered that normal serum in combination with extract will deviate a certain amount of complement, and the distinguishing property of syphilitic serum is its ability to deviate more of the latter. Consequently a standardisation of antigen is necessary in the search for that amount which will cause a reaction with syphilitic serum, but not with normal. The methods used vary with the different workers, but estimations are usually based on the amount of extract which will deviate a certain "minimal haemolytic dose" of complement in the presence of syphilitic serum and of normal serum. Some authorities vary the amount of this extract in the test proper to give quantitative reports believing that the strength of the reaction

is in inverse proportion to the amount of the antigen which gives a positive reaction. Ko~~l~~mer denies this, however, and considers that no reliance can be placed on such methods (47).

C. The complement.

Complement is present in every fresh serum but that of the guinea pig has been proved to be the richest source and the most suitable type for reacting with sensitised sheep's cells; this has been demonstrated in comparative investigations by Kolmer and his colleagues.(48). and by Noguchi (49). A fixed amount of serum (.05 cc.) was used by Wassermann and his collaborators in the original test, but owing to the variability of the complement content in a given volume of serum it also has to be standardised using increasing dilutions against a sensitised cell system (50). The "minimal haemolytical dose" (M.H.D.) of complement is the smallest amount which will cause complete haemolyses in a given concentration of sensitised cells and 3 M.H.D. is used by Harrison as his minimum in the test proper; he also uses a larger amount to give a quantitative analysis (51). thus agreeing with Browning and Mackenzie in their complement unit method (52). viz. they fix the amount of antigen and serum in their test and vary the amount of complement for quantitative results.

D. The Haemolytic System.

The cells employed are usually sheep's red blood corpuscles, but Noguchi claims advantages for human cells and Browning & Mackenzie prefer those of an ox- the matter is apparently immaterial for practical purposes, but whichever type is used it is necessary to immunise an animal against them (for convenience usually a rabbit). The titration of haemolytic amboceptor (i.e. rabbit's serum), and the strength of the suspension of cells used are procedures concerning which there is great difference of opinion, but which are purely technical and are questions for the bio-chemist and not the clinician. (53).

From the above it may be seen that even those brief notes point to a morass of dissenting opinion concerning the fundamentals of quantitative analysis. But as regards the degree of syphilitic infection (if we may be excused the phrase) we may summarise the principal methods under the following four headings:-

1. The complement Unit Method. of Browning and Mackenzie modified by Harrison and advocated by Medical Research Council No.1. where the variable factor is the amount of complement used.¹⁾

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1. Used by the British Venereal Disease Service. Alcoholic Cholestrinised Human Heart Extract is employed with a sensitised sheep's cell haemolytic system and two variations in the dilution of complement; known normal and syphilitic sera act as controls.

2. Serum dilution methods of which Kolmer's is probably the most satisfactory. A series of dilutions of serum are used the complement and antigen remaining constant.
3. Antigen dilution methods where variations in the dilution of antigen extract only, forms a scale. These procedures are not popular as it has been shown that the strength of an antigen is not always proportional to the dose.
4. The one-tube method of Wassermann¹⁾ is really a qualitative rather than a quantitative method; although it yields evidence of the presence of syphilitic antibody it gives only a rough indication of the amount. All the re-agents are present in a constant volume and results are interpreted by the degree of haemolysis as estimated by the observer.

The Precipitation Tests.

A number of precipitation tests are in use which will be briefly mentioned in the following paragraphs; these originated, as far as a reliable test for Syphilis was concerned with the work of Sachs and Georgi (1918) (54). who founded their procedure on observations that a precipitate was formed when syphilitic serum was mixed with an antigen of cholestrinised alcoholic heart extract.

Various dilutions of serum were introduced by Dreyer

1. German Public Health Service.

and Ward (55), and readings were made according to the amount of flocculation in the tubes. The results were fairly promising, but the simplicity of the technique is more than balanced by the difficulty in determining the presence or absence of a true precipitate in some cases. A strongly positive Sachs-Georgi might be taken for evidence of Syphilis, but as non-syphilitic sera comparatively frequently shows slight flocculation, there is a large indeterminate zone where interpretation is indefinite (56). Taniguchi and Yoshinari after investigating a series of 1575 cases point out that discrepancies between the Sachs-Georgi and the Wassermann Reaction are most marked in cases which have undergone treatment, and this is mainly due to the occurrence of a positive Sachs-Georgi where the Wassermann Reaction is negative (57).; the converse was true, however, in several cases, and Browning and Mackenzie consider that this might in part be due to a different reacting globulin fraction of the serum in the two tests as demonstrated by Mackie (57).

The most generally used modification of the precipitation tests to-day is that introduced by Kahn who employs as an antigen an alcoholic extract of ox heart with the addition of .6% cholestrol. He introduces a quantitative element by a series of dilutions of this antigen with saline, and uses a constant volume of serum in each tube. Readings can rapidly be made, but Kahn emphasis throughout

his book the importance of detail in technique and of adhering to a strict routine if results are to be satisfactory. He considers that his test "is of equal sensitiveness to a Wassermann Reaction in which a cholestrinised antigen and 18 hour fixation are employed. The results further indicate that the test possesses a high degree of reliability as a diagnostic agent in Syphilis" (58).; and in this he is borne out by the comparisons of The League of Nations Serological Conference (Copenhagen 1928), where it ranks higher than any of the complement fixation methods both as regards sensitivity and specificity. Although most laboratories use the test as confirmation to the Wassermann Reaction it has not gained the reputation of the latter in this country, probably owing to the fact that any slight aberration from the delicate technique in preparing the re-agents and conducting the test discountenances the results; in addition the reaction requires thoroughly experienced reading for satisfactory interpretation.

Many other precipitation tests have been devised but none have such a universal recognition as those mentioned; the best known are perhaps those of Vernes, and Muller, and the slide test of Kline - the last having the advantage that it can be done in an ordinary consulting room within twenty minutes of first seeing the patient; its utility, however, is confined to excluding Syphilis.

The Luetin Reaction

Following on the introduction of the Tuberculin Reaction in Tuberculosis, Noguchi conceived a dermatological test in Syphilis, using his cultures of Trep. Pal. and injecting solutions of the dead organism into the skin of the patient. He recognised three varieties of positive reaction. 1. The Papular form where an indurated papule appeared within twenty-four to forty-eight hours after the injection, reaching its zenith in four days. 2. The Pustular form where the papule becomes pustular about the fourth day. 3. The Torpid form where the papule disappears within four days to light up again on the 10th day or later. (59). This simple test was hailed with enthusiasm by the profession on Noguchi's description of his experimental results where he declared that although the reaction was indeterminate in primary, secondary, and Cerebro-spinal Syphilis, it had a far greater sensitivity than the Wassermann Reaction in tertiary, latent, congenital, and treated cases. These results were substantiated by many investigators, and in several of the series quoted with suitable controls the Luetin test was said to be 100% positive in tertiary cases (60); but as Stokes points out those workers' desire for such a promising key to the diagnosis of Syphilis apparently ran away with the unbiased estimation of their observations, and they omitted to give due

consideration to their controls (of culture medium). In consequence most of the early literature as regards the specificity of the test is valueless, and positive reactions were recorded later following the administration of bromides and iodides in the known absence of Syphilis. Again Corper, Gekler and Sweany found that out of 170 cases in a tuberculosis sanatorium 47% reacted positively to the Luetin test, but not to the Wassermann (62). Moreover Stokes demonstrated that patients with late Syphilis displayed a similar phenomenon on the injection of Agar (Hydrosol) alone, and considered that the test had no scientific foundation being merely a reaction of the sensitive skin of a Syphilitic to the impurities of the preparation. (61). The point at issue resolved itself into a question of whether Noguchi's culture contained the true organism of Syphilis or not (vide section 2A). and more recently preparations derived from the testes of injected rabbits, and undoubtedly containing the *Trep. Pallidum* have proven very unsatisfactory (63). Notwithstanding this adverse criticism, Noguchi's Luetin test may possess in certain cases considerable diagnostic value; of these the most favourable would appear to be diseases simulating congenital Syphilis or late acquired Syphilis, where the Wassermann Reaction is negative. Browning and Mackenzie declare that "a negative reaction under these circumstances would go far to exclude Syphilis

while a positive reaction would strongly support a syphilitic origin provided that the case had not recently undergone treatment with iodides (64)."

Lees is of the opinion that only the pustular reaction should be taken as diagnostic and confines his use of the test almost entirely to hereditary syphilis (65).

It may be remarked in conclusion that in spite of Stokes' critical aspersions the results of the Luetin test agree with modern opinion and theories on immunology, where an allergic response, e.g. the Cutaneous phenomenon under discussion, is thought to be the result of an antigen-antibody reaction on, or in the cells, which have removed the antibody from the blood and in some way fixed it themselves; or in other words the allergic state is associated with the presence of antibody fixed in the tissue cells, but absent from the circulating blood (66).

Thus if we were to agree that the syphilitic antibody was the same for the Wassermann Reaction and the Luetin Test an explanation would be offered at once for the inverse sequence of their positives. But it must be admitted that such conclusions are based on a number of possible, if not actual fallacies, any one of which if proven, would confuse our hypothesis past redemption. We must, therefore, leave the matter still at avisandum and await fresh evidence to lay before the court.

The multiplicity of the serological tests for Syphilis has led many authorities to plead for a standardisation of one procedure, the reports of which might be intelligible to the general practitioner of medicine without any special acquaintance with this branch; the clinician desires a plain "yes" or "no" to his request, and is none the better for having imposed on him a mass of hieroglyphics whose elucidation might well cost him a weary hour. As far as Britain is concerned this necessity has been met by the introduction of the standard test by The Venereal Disease Services whose reports ($++$, $+$, or \pm ⁶) are now well recognised by every member of the profession, and the significance of these results should be appreciated by all. But for the specialist, the syphilologist and the serologist does not the very multiplicity of the procedures indicate a healthy future for the science? Have we not in these tests a whole field for clinical and serological research which will be mutually advantageous? And do they not form the grounds for dispute, argument, and speculation which are the lifeblood of any study from metaphysics to venereology? It may be that one day we shall know all about the diagnosis of Syphilis, and have a perfect test for its presence in all its phases, but until that day dawns, and it is far distant, it behoves us to remember that evolution has never progressed by a process of

specialisation, and that the branches of the tree of knowledge bear the leaves which are vital to the growth and wellbeing of the parent trunk.

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Section 4.TREATMENT.

When one considers the bludgeonings of surgery in carcinoma, the therapeutic impotence of neurology, and the half hearted measures employed in cardiology, the Syphilologist may be excused a mild glow of satisfaction in his well stocked armamentarium; he has a treatment for Syphilis, which although by no means perfect, yet offers to his patient a prognosis of reasonable assurance, and whose fundamental aim is to eradicate the actual cause of the disease and not merely to prolong a life of incapacity and often suffering; indeed such is the renown of this Syphilo-therapy that one of its present weaknesses is the inclination to commence a routine treatment with the arylarsonates on the diagnosis of Syphilis, much as one puts a case of pneumonia on a temperature chart, Now in any form of treatment which has acquired specificity for a certain disease a skeleton outline of the procedure is a necessary basis for the proper conduction of a case, but an elasticity is necessary in its administration. Thus in Syphilis the so called "Courses" of treatment as detailed in the text-books are invaluable as a guide to the student, but it is mere folly for the therapist to adhere to them too closely; mathematical exactitude is never applicable to the reactions of the living organisms,

and not only must we take into account the extent and site of the pathological lesions, but an estimation of the patient's general constitution and physical health must be made before exhibiting drugs of such potency and toxicity as those used in Syphilis; and it is here that the skill of the physician, founded on experience and painstaking observation differentiates him from a robot with a syringe and an ampoule of novarsenobenzol. However rationalised a treatment may have become, (and we sponsor rationalisation in medicine wholeheartedly up to a point), the human element is a quantity which cannot be exactly measured on a numerical scale, but requires an intelligent, almost intuitive estimation, and a realisation of this fact would go far to increasing the efficacy and safety of syphilitic therapy and to stimulating professional interest in it.

The Arylarsonates.

The mode of action of the Arylarsonates.

Ehrlich himself endeavoured to explain the spirochaeticidal properties of the arylarsonates on his "Receptor" theory, postulating the OH and NH₂ groups as haptophores (i.e. anchoring the molecule to the organism) and the arsenical radical as a toxophore (i.e. producing destruction of the organism) (1), but since his whole "Receptor" theory has now gone by the board (2) as an ingenious and picturesque fabrication, his explanation concerning the action of Salvarsan has more or less

gone with it. According to the more recent work of Voegtlin and Smith, it seems likely that the really toxic agent for the Treponemata is "Arsenoxide", which is a product resulting from the oxidation of the arylarsonates in the body (3). Other authorities believe it possible that the drug by destroying a number of Treponemata releases endotoxins which stimulate the formation of antibodies inimical to the organisms; still others that the drug itself produces the antibodies from its action on the tissues. Fashionable theories implicating the reticulo-endothelial system have not been omitted, but there is little experimental evidence to substantiate any of these hypotheses (4).

The comparative therapeutic efficiency
of "606" and "914" preparations.

In attempting to estimate the therapeutic efficiency of these drugs four criteria must be considered - 1. The disappearance of Treponema Pallidum from primary and secondary lesions.
 (2). The rapidity of healing of surface lesions.
 (3). Their effect on the blood Wassermann Reaction, especially in early Syphilis.
 (4). The ultimate clinical results of treatment.

The first two of these considerations need not delay us long; as regards the first - there is a general concensus of opinion that with ordinary therapeutic doses "606" is more effective in causing the disappearance of the organism than "914", but that any of the arylarsonates, with the

exception of Bismarsen, will have this effect in twelve to twenty-four hours. (5). The rapidity of healing of the surface lesions in primary and secondary syphilis is again accelerated by the use of Salvarsan in preference to Neo-Salvarsan, the average number of grammes of the former being 1.3 and of the latter 3.8 in a series of Cannon and Karelitz; the average number of injections was 2.7 and 5.8 respectively. Therefore, when allowance is made for the increased percentage of arsenic in "606" it is found to be nearly twice as potent as "914" (6).

With reference to the two types of drug on the Wassermann Reaction, Stokes gives an excellent summary of the experimental evidence to date. The average time for the reversal of the Wassermann Reaction in sero-positive primary Syphilis under "606" was 38.2/10 days, using 3.83 Gms. of the drug in seven injections, while "914" required 5.54 Gms. in ten injections over a period of 81.6/10 days; in early florid Syphilis the time, number of injections, and amount of the two drugs used, was slightly increased in the same ratio (7). Stokes quotes the results of the Co-operative Clinical Group which investigated a series of cases in all stages of the disease, and who underwent all systems of treatment (continuous, intermittent and irregular), and came to the conclusion that Salvarsan was about one and a half times as effective as Neo-Salvarsan, each being used in its individual

therapeutic doses (7). The two drugs approached more nearly to equality however, when used in conjunction with the heavy metals and moreover although the disparity in the percentages of reversal to sero-negative was pronounced over a period of three months, there was little or no difference over a period of twelve (8). - Neo-Salvarsan therefore although a slow starter was a strong finisher. Stokes summarises the situation by saying that, although Salvarsan must have preference to Neo-Salvarsan as far as potency is concerned, the disparity between the two tends to disappear when used in conjunction with a heavy metal and over a prolonged period (8).

There can be little doubt therefore that from a "scientific" point of view the "914" preparations must take second place to the original "606", but let us compare the two from a clinical, i.e. practical, standpoint. When administered by the intravenous route Harrison admits that "606" has a great therapeutic effect that "914", but considers that this is due to its slower excretion and that when exhibited intramuscularly "914" is equally potent although naturally not so rapid in its action (9). Moore on the other hand is of the opinion that the superiority of the original preparation in terms of ultimate satisfactory outcome and of relapse is apparent, and quotes figures from the Co-operative Clinical Group where the incidence of relapse was 12.4 with "606", as

opposed to 16.4 with "914", the cases undergoing continuous treatment (10).; the question of dosage and duration of treatment, however, has been left out - unfortunately in view of Stokes' consideration that the disparity of the two drugs as regards their serological effect is diminished when the period of their administration is prolonged. Schamberg and Wright after examining the clinical data as to their comparative merits conclude that "Arsphenamine produces superior clinical results to Neo-arsphenamine and yet Neo-arsphenamine is used to an enormously greater extent by the profession than Arsphenamine" (11)., the reason being, of course, the simplicity of administration. They consider that although therapy with "606" compounds will doubtless be continued by specialists and in certain individual cases, "914" used concurrently with Bismuth gives sufficiently satisfactory results to ensure its general popularity if the physician perseveres with it. In addition to their therapeutic efficiency we must take into consideration the relative toxicity of the two drugs, and most authorities agree that in general terms the reactions are fewer with the more modern than with the original, despite the statistics of recent years which rather incline to the view that the comparative toxicity of Salvarsan has been overestimated (8). In brief then we may concede that "606" is a more potent drug than "914", but that from the point of view of practical politics,

where usually one's ideal must be the greatest good for the greatest number, the simplicity of the administration of the latter must outweigh the therapeutic superiority of the former, which necessitates a tedious and exacting technique.

The more recent Arylarsonates.

A few notes concerning some of the more recent productions will be given here, with special reference to authoritative opinion on them.

A. Sulpharsphenobenzene (Sulfarsenol).

An additional radical containing sulphur has been substituted in this drug for an amino group of Salvarsan. Although it may be administered intravenously its greatest therapeutic effect is obtained by the intramuscular or deep-subcutaneous route, when it exerts a powerful action against Syphilis (12). and if the technique of administration is satisfactory little or no pain is experienced according to Lees (13), although Schamberg and Wright consider that this is the main objection to the drug. They agree with Harrison that intramuscular therapy is probably more efficacious (14). but in view of their observations concerning the discomfort produced, they confine their use of Sulfarsenol to congenital Syphilis, and those cases in which the veins are too poor for intravenous therapy (15). Personally I have given a large number of injections of Sulfarsenol by the deep-subcutaneous route without any marked complaint. Moore's objection to the

drug in routine anti-syphilitic treatment is based on the frequency of its producing dermatitis and the blood dyscrasias (16), and Stokes for the same reason has been forced to condemn it, although he admits that statistics as regards the toxicity are so diametrically opposite, that it is likely that the composition of the drug is variable (17).

This, I should think, is more than probable as the generally favourable reports in this country are in striking contrast to American opinion.

B. Silver-Salvarsan.

The exact chemical formula of this drug, introduced by Kolle during the War, has not yet been satisfactorily proven, but the basis is the introduction of a silver molecule in one or other of the Salvarsan radicals (18). The underlying theory of its use is a combination of heavy metal with Salvarsan, in the hope that the therapeutic advantages of each will be united in one preparation. Kolle himself considered that the silver acted as a prop to the action of the arsenic, inhibiting the multiplication of the Treponemata while the arsenobenzol molecule exerted a direct spirochaeticidal action (19).

Although it has found popularity in Germany its adoption in this country and America has been confined to experimental work and the treatment of individual cases. Opinion differs as to the advisability of administering Bismuth or Mercury with it, which would appear to be

unnecessary if there is any foundation in the theoretical conception of its action. (19).

Harrison uses it only in cases of neurosyphilis where its efficacy is thought to be superior to "914" or "606" (20).

The complications of its administration are those commonly seen after any of the arylarsonate compounds with perhaps an increased incidence of pyrexia and dermatitis. In addition, occasional cases of argyria have been recorded, and Spiegel states that a total of 8 Gms. of Silver-Salvarsan should not be exceeded if this disturbing and permanently disfiguring complication is to be completely avoided (21).

C. Bismuth Arsphenamine Sulphonate (Bismarsen)

Conceived on the same principle as Silver-Salvarsan and introduced by Raiziss (22) in 1925, this drug is a combination of Bismuth and Sulpharsenobenzene which has been reported on favourably by many American authorities, including Stokes, but which has not received much recognition in Britain up to date (23). It is administered intramuscularly twice weekly in doses of .2 Gms., and Stokes emphasises the importance of prolonged therapy if the best results are to be obtained; its slow spirochaeticidal action in primary and secondary lesions compared with "914" and 606" preparations, has discredited its use to some extent in early Syphilis, but it is worthy of note that relapses

are believed to be fewer when this therapy is adopted. The field of choice for its use appears to be latent and visceral Syphilis, where its slow and steady action is ideal, and where its practical ineffectiveness against the serological changes is a matter of note great import (23).

Local pain and tenderness at the site of injection seems to be the commonest complication of Bismarsen, but most of the other arsenical reactions have been reported, and there is perhaps an especial tendency to the blood dyscrasias (23).

D. Tryparsamide.

A pentavalent arsenical this drug has won for itself an increasing number of adherents as its use has become more generalised in neuro-syphilis. Although its spirochaeticidal properties are negligible compared with other arylarsonates, and although it is useless in the treatment of somatic Syphilis, it has a remarkable therapeutic efficiency in neuro-syphilis (24), which is most probably due to its power of penetrating the nervous system through the meninges. Clinically the effects of the drug are most encouraging to the patient, as it has a general tonic effect as well as a specific action on the syphilitic lesion; indeed Brown and Pearce believe that the former is its most important action and that "it is the opportunity afforded for inducing an involution of the infection by reinforcing natural processes of resistance" which has gained for

Tryparsamide its well earned reputation (25).

There is little or no effect from Tryparsamide on the blood Wassermann Reaction, but the pathological condition of the cerebro-spinal fluid in these cases is definitely benefited especially as regards the cytobiology. In a series of Moore, Robinson, and Lyman, among sixty-eight patients with parenchymatous neuro-syphilis the spinal fluid became completely normal in 22%, and markedly improved in 40%, while in the meningovascular group 69% became completely normal. The courses employed were eight to sixteen injections of 3 Gms. of Tryparsamide (26). Solomon and Veits report the reversal of the Wassermann Reaction in about one half of their cases of Tabes dorsalis (26).

The particular *bête noir* of Tryparsamide therapy is the production of optic atrophy and frequent ophthalmoscopic and visual-field examinations are advisable throughout its administration. The presence of optic atrophy as a complication of tabes dorsalis or syphilitic retro-bulbar neuritis, is usually considered to be a contra-indication to the use of the drug (27)., but the Edinburgh School, with commendable logic and courage, actually treat this condition with Tryparsamide. They argue that the two aetiological factors of the optic atrophy are quite different and that there is no reason to believe that a summation of their activities will be produced, but that on the contrary, beneficial results will accrue from the exhibition of a drug

which is known to be generally antagonistic to a neuro-syphilitic process; and moreover since tabetic optic atrophy is progressive to the point of complete blindness no great additional harm can come from the trial of this therapy, and there is a definitely logical probability of benefit. Their results as judged by careful and repeated examination of the visual fields throughout treatment are decidedly encouraging (28)., which would rather point to the optic atrophy of Tryparsamide being completely dissociated from any stimulant effect of the drug on the diseased process as some authorities declare (27).

The Toxicology of the Arylarsonates.

The more important of the complications met with during therapy with the arylarsonates will be discussed in the following pages, and especial reference will be made with regard to the theories concerning their mechanism.

A. The Jarisch-Herxheimer Reaction.

Originally confined to the intensification of the secondary rash which often results at the onset of treatment, the Jarisch-Herxheimer Reaction has come to mean any aggravation of a syphilitic lesion, (and its symptoms and signs), which follows the initial injections of one or other of the anti-syphilitic drugs, especially the more potent arylarsonates. Thus we find that eight to twelve

hours after the first injection of "606" or "914" particularly if given intravenously, tabetic or osseous pains may be increased, cardiac distress may be more pronounced, cutaneous gummata may appear more inflamed, etc. etc. according to the site and nature of the lesion of which the patient complained in the first place; in addition systemic disturbances may be present such as pyrexia, headache, malaise, etc. The cause of this reaction is not yet known definitely, but Ehrlich (29) believed that it was due to a dose of the drug which was insufficient to kill the organism, and resulted in a temporary stimulation of its activity; in this he was supported by Iverson (29), who found that with small doses of Salvarsan in cases of Relapsing Fever, there was initially an actual increase in the number of spirilla in the blood, and Browning's observations in the treatment of experimental Trypanosomiasis with methyl violet were similar (29). But on the other hand we find that the Jarisch-Herxheimer Reaction is less pronounced when small doses of Salvarsan are administered or when the intramuscular route is employed, so that most authorities consider that the phenomenon is not due to the stimulation of the treponemata but to their rapid destruction with a liberation of endotoxins, which would naturally increase the inflammatory reaction in the tissues involved. This view is held by Moore (30), and both he and Stokes (31) compare the reaction to that of tuberculin in tuberculosis on symptomatic

grounds, but deny that there is any fundamental immunological analogy. Apropos of this however, Browning and Mackie (32) consider that "the phenomenon of super-sensitiveness of tuberculous patients to tuberculin is due to the combination of the injected antigen with molecules of antibody resident in the tissue cells", this being true of course for the focal and systemic reactions as well as the local. Now I see no reason why the endotoxins of the *Treponema Pallidum* should not be as potent antigens as those of the *Tubercule Bacillus*, and an explanation on an allergic basis appears to me to be as applicable to the one phenomenon as to the other, the only difference being that the antigen of the Herxheimer reactions is produced by the destructive action of a drug on the organism in vivo.

Apart from the theoretical interest of the Herxheimer "flare up", its clinical importance depends entirely on the anatomical site and physiological function of the organ attacked by the syphilitic process. Thus no especial care in this direction is required in such lesions as the generalised secondary rash or cutaneous gummata, but grave results might easily ensue on too enthusiastic administration of the arylarsonates in mesaortitis, gumma of the larynx, and optic atrophy, where a sudden exacerbation of the condition might well cause coronary artery occlusion, suffocation, or complete blindness respectively.

These perhaps are the most important conditions in which the Hexheimer phenomenon must strike a note of warning, but other examples are obvious in clinical practice, and indeed it is as well to hasten slowly in the therapy of all visceral Syphilis (33).

B. The Nitritoid Crisis.

The Nitritoid or anaphylactoid reaction, so called from its clinical similarity to the effect of an injection of amyl-nitrite, or anaphylactic shock, embraces a multitude of symptoms of cardiovascular and respiratory type, which vary from a mild flushing of the face and neck, to extreme cardiac distress, with "asthmatic" breathing, and even complete collapse and pulselessness.

The cause of these symptoms usually occurring during or immediately after an injection of the arylarsonates presents a problem which has not yet been solved and around which argument is still rife. The resemblance of the symptoms to anaphylaxis has led some writers to assume that the reaction is of this type, but as the Salvarsan Committee of the Medical Research Council (34) points out the evidence for this is very slender, and in spite of the theories of Swift and Moore, and Keidel (34) there is abundant evidence that the immediate reaction may be produced by the primary injection, thus discountenancing any suggestion of previous sensitisation. Physical conceptions of the anaphylactic mechanism were put forward by Bezredka and Strobel, and by

Danysz (35) - the former considering that there was a precipitation of the drug in the blood stream, while the latter contended that the serum proteins themselves were precipitated by Salvarsan and confirmed Fleig's (36) original observation that a precipitate is found in the pulmonary capillaries when experimental animals are subjected to this reaction. Stokes was originally a strong advocate for this precipitation theory, and considered that however it was accomplished, it was the exciting agent in the production of an "anaphylotoxin" which produced the reaction (35); more recently, however, he has been impressed by the work of Oliver, Douglas, and Yamada (vide infra). The fact that the incidence of the reaction frequently occurred with certain batches of the drug lead to the supposition of an impurity being present, and the Salvarsan Committee quote a series of Glaser and Langer where sixteen cases receiving .45 Gms. of Neo-Salvarsan as a third dose all suffered from nitritoid symptom (34). Further, it has been shown by Hirshfield, Hyman, and Wanger that rapid injection of Salvarsan into animals is followed by an immediate train of symptoms including salivation, dyspnoea, lessened coagulability of the blood, fall in blood pressure, and even death. The reactions did not occur in animals in which the liver had been removed, and the authors consider that the cause is to be found in the liver cells where some substance, possibly histamine, is liberated or escapes destruction (37). All authorities, including

Harrison (38) and Lees (39) stress the importance of too rapid administration of the drug in promoting the reaction, and the latter agrees with Stokes that "desensitisation" by a minimal dose of the drug half an hour before the administration of the major portion, enables one to continue therapy safely (39).

The most outstanding work of the present day on the subject is that of Oliver, Douglas, and Yamada, who have shown that vascular injury-capillary dilatation and injury to their walls - underlies the reaction; they consider that this is caused by red blood cell agglutination with consequent capillary thrombosis. As Stokes says this explanation would accord with the appearance of an idiosyncrasy in a patient after repeated injections, and with the fact that some individuals react with the primary injection, the former's red blood corpuscles acquiring a hypersensitiveness which was present in the latter's in the first place. It also accords with the occurrence of consecutive reactions with one consignment of the drug where some impurity might be present in the various samples and be the cause of the agglutination. The agglutinative action is moreover proportional to the dose of the drug and the rate of its administration (40). The beneficial effects of adrenalin, if we agree with this hypothesis, would be due to its dilating the bronchioles, increasing the tone of the arterioles, raising the blood pressure, and thus combating the

shock; there would be no necessity to concern ourselves with Hirano's theory that there was some interaction between the adrenals and Salvarsan (41), a theory founded solely on the therapy of the condition and rather suggestive of putting the cart before the horse, which although by no means unique in medicine is usually unsatisfactory when no confirmatory evidence is forthcoming.

C. Encephalitis Haemorrhagica.

The striking nature of this complication of arylarsenate therapy rather than its frequency has been responsible for the attention it has received in the literature. It generally occurs 24 to 48 hours after a second or third injection with the sudden onset on unconsciousness, and less frequently with prodromal symptoms of nerve irritation such as headache, lack of concentration, clonic spasms, etc. (42). Histological examination shows the presence of diffuse areas of haemorrhage which are in reality pericapillary extravasations (43). The incidence of the condition is fortunately rare as it is nearly always fatal, but Lees points out that this high mortality is probably due to a mistaken or delayed diagnosis, confusion arising with simple apoplexy, uraemia, acute alcoholism etc., and appropriate treatment being consequently postponed (42).

The mechanism of the lesions appears to

be an injury to the capillaries of the brain, but how and why this occurs is still disputed; two schools of thought, however, are quoted by the Salvarsan Committee of the Medical Research Council:-

1. The condition is really acute cerebral Syphilis intensified as a result of the injection (Herxheimer Reaction).
2. It is a direct result of the Salvarsan, possibly in persons unduly susceptible to the drug (44).

Now as regards the first of these explanations, there is no record in the literature previous to Salvarsan medication of such a fatal complication of acute cerebral Syphilis, although the clinical manifestations of the latter were fully recognised and described with little variation from our present conception of this type of Syphilis. Moreover when we consider that several cases of haemorrhagic encephalitis have been recorded following therapy by Salvarsan or its substitutes for diseases other than syphilis, we see that the syphilitic process can have little, if anything, to do with the production of such a fatality. Less, whose experience of this condition is quoted by several authors, describes its occurrence, following the administration of a Salvarsan product in cases of Disseminated Sclerosis and Hodgkin's Disease where no evidence of syphilis was present either clinically or serologically (45). Finally there is no mention in the literature that

such cases uniformly demonstrate syphilitic involvement of the central nervous system before the occurrence of the encephalitis. It may be that Syphilis is a predisposing factor in the production of encephalitis haemorrhagica much as alcohol (46), endocrine deficiency, and influenza (47) may create suitable conditions for its occurrence by lowering the general resistance of the patient, but there can be little doubt when we face the facts that the arylarsonates, or their toxic products, are the actual cause, and not the syphilitic process. Ehrlich himself considered that the phenomenon was due to a toxic oxidation product of Salvarsan (47).

The mechanism of the condition, as we saw, was essentially a damage to the capillary endothelium of the cerebral vessels, with consequently numerous small haemorrhages and hyaline thrombi, and an extensive oedema of the brain, which as Stokes points out is very similar to the oedema of delirium tremens (48). Now this pathological picture is by no means specific, similar lesions having been described many years ago in connection with fatal cases of malaria, fat-embolism of the brain, carbon-monoxide poisoning, and more recently during the War with phosgene gas poisoning and war nephritis (49). Von Marschalko and Veszpelemy described a very typical case of haemorrhagic encephalitis following Salvarsan in 1912, where most of the lesions were found in the pons Variollii, corpus callosum, temporal lobes, and lenticular nuclei, and it is interesting

to note with regard to our discussion of the aetiology, that they remarked the scantiness of the leucocytes and the complete absence of changes associated with inflammation (49). No thrombi have been found in the other viscera but Jerseld has reported the presence of multiple small haemorrhages in the liver, spleen, kidneys and lungs of a fatal case (50). Oedema of the brain was a marked feature of Stuhmer's cases, resulting in one instance in an acute internal hydrocephalus (50), and it is this oedema no doubt which is the principal reason for the majority of the fatalities, since by increasing the intracranial pressure it will compress the vital centres of the medulla against the base of the skull. Hence the therapeutic benefit of lumbar puncture and venesection (and adrenalin), advocated by Schamberg and Wright for the relief of intracranial pressure (51).

D. Dermatitis.

The arylarsonates are prone to produce a wide variety of skin reactions ranging from mild and ephemeral eruptions of no importance, to the grave and sometimes fatal exfoliative dermatitis. The mechanism responsible for the different lesions probably varies according to their morphology, and Moore who has performed extensive research on this subject classifies them all under three headings:-

1. The Angioneurotic Reaction Syndrome, under

which he includes the urticarial lesions.

2. Those lesions associated with a concomitant infection, of which he considers the early erythematous, scarlatiniform, and herpetic eruptions to be types.

3. The sensitisation phenomena including macular; papular and vesicular rashes, and most important of all exfoliative dermatitis (52). Only this last will be discussed here, but it must be remembered that any of the other skin lesions may precede or accompany the major calamity.

Although there is general agreement that the arylarsonates are the prime factor in the causation of exfoliative dermatitis, there has been much theoretical discussion as to the manner in which they produce it, and the type of case in which we might expect it. The modern trend of opinion appears to ascribe the reaction to an allergic phenomenon, the skin being hypersensitive either from a personal idiosyncrasy or from previous sensitisation; the latter according to Stokes may be acquired either by previous injections of Salvarsan or by the presence of septic foci in the body with absorption of toxic proteins which sensitise the cutaneous tissues to subsequent arsenical therapy i.e. the allergy is not specific. (53). Lees also stresses the importance of the presence of intercurrent infection, especially the focal variety, and mentions in addition that practically all of his cases suffered from a previous dermatosis (54). In this Stokes agrees with him,

and seems on the whole to favour the view that exfoliative dermatitis is found in patients with an eczematous diathesis which will become clinically evident in the presence of an irritant, and in certain individuals such a reaction will result from the injection of one or other of the arylarsonates (53); in other words the tendency is born with the individual and not thrust upon him like greatness upon Malvolio. The strength of the argument is greatly increased when one remembers the frequency of exfoliative dermatitis apart from the exhibition of arsenic. Moore considers that "dosage, technique of administration, impurities in the drug, and manufacturer's lot of drug employed, play no basic part in the development of the reaction", and although he is a strong supporter of the allergic theory, in his opinion the hypersensitiveness is specific, and acquired by injection of the arylarsonate group only, but he is unable to explain the rare occurrence of the reaction after the primary injection (55). In contradistinction to these theories there is a school of thought which believes that the dermatitis is due to the direct vasculo-toxic action of arsenic, and in support of this Osborne has demonstrated an accumulation of arsenic around the cutaneous capillaries and a disappearance of the drug relative to, and coincident with, clinical improvement (53). In this connection Hoffmann considers that the excretion of the drug is impeded by damage to the liver, and that the arsenic is therefore apparently

concentrated in the cutaneous tissues (53) (Is it possible that "Allergy", like the Opsonic Index in "The Doctors' Dilemma", is becoming too fashionable a "mode", and will eventually tread the well-worn path to limbo, like so many of its predecessors?)

The blood picture in cases of exfoliative dermatitis presents peculiarities which will be discussed below, but it is worthy of note here that an eosinophilia is usually marked (up to 60%) (56), which on the basis of analogy would rather favour the sensitisation explanation of the phenomenon. To sum up we may say that the weight of evidence leans towards an allergic reaction as being the true cause of the condition, but that the question is not settled, and that the why and wherefore is likely to remain obscure until "Allergy" is thoroughly understood; at present it is little more than a shibboleth as far as scientific understanding is concerned.

Studies of the clinical application of cutaneous test procedures to detect hypersensitivity to the arylarsonates, have been overshadowed by the observation of certain authorities that injection of even minute quantities of the drug into the skin (e.g. leakage during an intravenous injection), may result in a sensitisation of the part, which in certain cases will form the starting point of an exfoliative dermatitis (57). In the test devised by Jadasshon the drug is applied to the unbroken skin, but even here hypersensitivity has been induced in isolated cases, so that these tests are looked at with some

dubiety by syphilologists in general (57). Moore, however, denies that the injection of small quantities of arylarsonate into the skin will cause this hypersensitivity (vide supra).

E. The Blood Dyscrasias.

Under this heading we will discuss those effects on the haematopoietic system which appear to be the result of a direct toxic action of the arylarsonates on the constituents of the bone marrow, and leave out of consideration the haemolytic action of "606" and "914" on the red blood corpuscles in the circulation, which appears to be relatively unimportant; the agglutinating effects of this group of drugs have been discussed under the nitritoid crisis.

According to Moore three types of reaction are recognised all of which it may be noticed, have their clinical homologues in general medicine, where no question of drug intoxication arises.

(a) Thrombocytopenia, (b) Granulocytopenia and (c) Aplastic Anaemia (58). In all these the clinical and blood pictures are indistinguishable from what we may call their "idiopathic brethren". Thrombocytopenia according to Moore always has a favourable recovery, and no special treatment is necessary (58). It would appear that the arylarsonates have the same effect on the blood-platelets as the reticulo-endothelium system in the idiopathic variety; either that or they render the platelets hypersusceptible to phagocytosis by the latter;

fortunately it is easier to stop the administration of the drug than to remove the spleen (59). Both granulocytopenia and aplastic anaemia due to Salvarsan or its derivatives run the usual almost universally fatal course if left untreated, but it is interesting to note that the mortality rate in the former has been reduced from 90% to 25% since the recent introduction of pentnucleotide therapy (68).

Of the drugs which are most toxic in this connection Sulfarsenol appears to rank first with Novarsenobenzol a good second, but whether or not the effect is due to the arsenic rather than the benzene radical is still undecided, both being known to have a depressing action on the bone marrow. Whatever the cause, however, the reactions appear to be much more common than is generally admitted and Stokes considers that "in all probability some degree of injury to the bone marrow is instrumental in bringing about the fatal termination of the acute arsenical poisonings with the arsphenamines associated with jaundice, purpura, dermatitis and other manifestations" (61). Apropos of this statement, the blood picture in exfoliative dermatitis as we saw was characterised by an eosinophilia, but in addition to this, in fourteen out of sixteen cases studied by Moore and Keidel, a well marked leucopenia involving the neutrophil polymorphs was present with an increase in the large mononuclear cells (62). In severe cases true aplastic anaemia has been recorded.

F. Post-Salvarsan Jaundice.

The literature contains such a mass of conflicting evidence as to the aetiology of jaundice occurring during the arsenical therapy of Syphilis that it is almost impossible to elucidate facts of any general significance. The classification adopted by the Salvarsan Committee of the Medical Research Council recognises three main types of hepatic accident (a) Early or "Benign" Jaundice. (b) "Late" Jaundice. (c) Acute Yellow Atrophy of the Liver - generally a sequel of "Late" jaundice, but occasionally occurring as a bolt from the blue at any period throughout the treatment (63). Now it would perhaps simplify matters if we adopt the aetiological classification of jaundice in general and consider all these types as toxic, as opposed to haemolytic and obstructive jaundice, assuming in accordance with present pathological opinion that they are stages in the same process, having the same pathogenesis and varying only in the degree of its intensity (64). Thus we might consider "benign" jaundice, like the so called "catarrhal" jaundice, to be an acute yellow atrophy in miniature (Eppinger) (65), the degeneration of the hepatic cells in the former case occasionally proceeding to complete necrosis in the latter, and the underlying pathology in both being a toxæmia of the liver cells. The problem we must now face is a consideration of the factors responsible for this toxic process and

whether they vary in different cases. The various casual possibility may be included under the following headings -

- (a) That the jaundice is due either to Syphilis or incidental infection.
- (b) That it is due to the arsenobenzols per se.
- (c) That the arsenobenzols, acting on a liver already damaged by Syphilis or some other infective process, produce clinical evidence of hepatic disease.

As regards the first of these possibilities the occurrence of jaundice as a manifestation of Syphilis is well recognised, occurring in the secondary stage as a "catarrhal" jaundice, whose fundamental pathogenesis is thought to be in the nature of a hepatitis, and where the obstructive element of biliary catarrh is now believed to be merely incidental, although possibly an additional factor in producing degeneration of the liver cells (65).

Acute Yellow Atrophy has also been recorded in the florid stage of Syphilis without any therapy whatsoever, while of the later manifestation syphilitic cirrhosis is a wellknown clinical entity, and one which might enter into the differential diagnosis as a cause of "late" jaundice (66). Supporters of the view that Syphilis, and not the arsenicals, is the main cause of hepatic symptomatology include Milian, who claims to have cured these cases by further injection of the drug, and who argues that they are in the nature of recidives. He points out

that the severe cases usually occur six to eight weeks after the cessation of treatment (the favourite period for neurorecidives), and are often accompanied with other symptoms of Syphilis such as mucous patches (67). His arguments are certainly convincing and probably true up to a point, but since there is no way of differentiating the aetiology of hepatic accidents clinically, be they due to the arylarsonates, Syphilis, or "idiopathic" causes, the only means of assessing the importance of the various factors is a study of the statistical evidence of the occurrence of jaundice in pre- and post- Salvarsan years. This the Salvarsan Committee of the Medical Research Council have undertaken and have come to the conclusion that jaundice and acute yellow atrophy have increased in frequency since the introduction of Salvarsan. They state further that heroic doses of the drug have been associated with an increased liability to these complications, and although they are unable to explain the frequently prolonged latent period they show that this was also present in cases of trinitrotoluene poisoning during the War, where the pathology was very similar (68). Hallam agrees that the arylarsonates are probably the main cause in the production of jaundice, and believes that certain lots are especially icterogenic, incriminating "914" preparations in particular. (69), while Strathy, Smith, and Hannah consider that mercury by producing a nephritis will act as a contributory cause when given in conjunction with an arsenobenzol (70).

Probably the most logical view is that which embraces all of them, viz. that while the arylarsonates may have a toxic action on a normal liver if given in large doses, this effect is likely to be greatly increased in a liver already damaged by Syphilis or "catarrhal" jaundice, even if these are sub-symptomatic. This of course would include the explanation offered for those cases of jaundice which occur just after treatment is initiated, where a Herxheimer Reaction is thought to be the mechanism of the condition (71). It would further explain the frequent occurrence of epidemics of Salvarsan jaundice, as the idiopathic variety is well known to occur thus. Illustrative of this theory, Todd reported thirty-nine cases of jaundice occurring in soldiers just after the onset of cold weather, and of these, twenty-four had been receiving "914", while fifteen were non-syphilitic (72). Lees mentions his impression that catarrhal jaundice is becoming more frequent in recent years, and indicates that this might be a possible factor in the increased incidence of the hepatic accidents of Salvarsan therapy (73). Of course, it is obvious that the converse of this hypothesis would be equally true, namely, that a liver damaged by arsenobenzol would prove a fruitful field in which another pathological process might flourish, and in this connection it may be noted that some degree of hepatic insufficiency is demonstrable by liver function tests in nearly

every case treated by a course of Salvarsan or its derivatives (74).

G. Albuminuria.

This is a comparatively rare complication of arylarsonate therapy and will be mentioned more fully under Bismuth.

Bismuth Preparations.

The Mode of Action of Bismuth.

As in the case of all other anti-syphilitic drugs, there is a considerable controversy over the method by which bismuth exerts its favourable action in the disease. Levaditi, one of its foremost exponents, expressed the opinion that it was directly spirochaeticidal in vivo, and quotes experimental evidence in its favour. He admits that bismuth preparations have little or no effect on the multiplication of trypanosomes or spirilla in vitro even when used in concentrations far exceeding those in which it must permeate the tissues, but when these very concentrations are incubated with liver tissue at 37° C. for three or four hours, the previously inactive mixture is found to be actively antagonistic and destructive to the organisms in question. Levaditi believes that there is an active principle

"Bismogene" in living tissue which, acting on bismuth or its derivatives gives rise to a substance which he calls "Bismoxyl" and which is directly spirochaeticidal (75).

Kolle, on the other hand, maintains that bismuth acts only as an inhibitor in the reproduction of the organism. He bases his view on his experiments with rabbits, where he injected "plugs" of bismuth into the animal's ear before inoculating it in the same site with *Treponema Pallidum*; the inoculation failed to "take" as long as the plug remained but a typical chancre developed within the usual incubation period after its excision (76).

Other biological effects of bismuth such as its action on the blood nitrogen etc. seems to have nothing to do with its therapeutic properties in Syphilis and need not be discussed here.

Therapeutic effect of Bismuth in Syphilis.

Clinically there is a mass of evidence to show that bismuth favourably influences the course of a syphilitic infection in all its stages, but since its action is slow compared to that of the arylarsonates, both as regards its sterilising and healing effects on the surface lesions, its solitary administration in primary and secondary Syphilis is not usually recommended (77). Levaditi, however, believes that there is less likelihood of recurrent syphilides when a case is persistently treated with bismuth preparations from the start, and considers the drug to be the equal of any of our anti-

syphilitic remedies; he further considers that its action on secondary syphilides is practically as rapid as that of the arylarsonates, and reports an especially favourable therapeutic efficiency on buccal mucous papules, in which he observed cicatrisation within four to five days; its effect on hypertrophic papules, roseola, and palmar syphilides was similarly encouraging, while headaches and osteocopic pains disappeared after the first injection (78). It is, however, in the field of tertiary Syphilis, especially in its visceral manifestations, and in those cases resisting arsenical treatment that bismuth finds its greatest therapeutic scope. In cardiovascular Syphilis its slow and steady action when administered intramuscularly is most serviceable, but even with bismuth careful dosage must be observed if a Herxheimer Reaction (often fatal in these cases) is to be avoided (79). The interval in treatment caused by hepatic accidents, such as jaundice following the arsenobenzols, is often successfully bridged by bismuth therapy, but in late Syphilis of the liver, Stokes again gives a word of warning as to dosage (80).

The drug has perhaps an especial reputation in neuro-syphilis, possibly because many of these cases have become resistant to treatment by the arylarsonates; localised lesions of the nervous system, according to Levaditi, show more pronounced benefit, but he also records an amelioration of symptoms in Tabes and General Paralysis of the Insane (81).

Early syphilitic meningitis responds quickly to the action of bismuth, and Peyrus believes that in cases of spasmodic syphilitic paraplegia a "restitutio ad integrum" may be hoped for even in cases which have resisted arsenic and mercury (82). Its mode of action in neurosyphilitic cases is doubtful since modern investigations have detected little or none of the metal in the cerebro-spinal fluid after its administration (83).

As regards its effect on the Wassermann Reaction, gratifying results have been reported both in early and late Syphilis; it is generally recognised that bismuth if administered properly will prevent a negative serological test in primary Syphilis from becoming positive, and will reverse an early positive reaction with ten to fifteen injections in a large proportion of cases; its action, however, is slower than the arylarsonates and in the opinion of some not nearly so definite (84). In the long standing positive Wassermann Reaction its action is variable, some remaining positive in spite of long continued therapy, while other cases which have remained "fast" under arsenic, reverse to negative after comparatively few doses, probably, as Stokes remarks, due to the change in the angle of attack (85).

Comparing the therapeutic effect of bismuth with mercury, Schamberg and Wright unhesitatingly place them in this order of precedence, but while acknowledging the superiority

of the more recent medicament, they consider that in the therapy of Syphilis there is still a place for mercury which, they point out, can be given by a number of avenues, and which is a most valuable drug for use in the intervals between courses (86); and in this, I think, most syphilologists will agree.

It will be seen from this brief survey of the therapeutic capabilities of bismuth, that the most logical procedure is to use it in conjunction with one or other of the arsenical preparations in the general run of syphilitic cases, thus attaining the swift spirochaeticidal action of the more potent drug with the slower and more prolonged action of the heavy metal. The only possible objection to such combined therapy would be an increase of the toxicity of one or both of the drugs when administered together and there is no indication in the literature¹⁾ that such a reaction occurs; indeed such combined treatment is almost universally acknowledged as our present ideal in syphilo-therapy, and Harrison examining a series of cases with regard to relapse, found that these were much less frequent in patients treated with an arsenical preparation and bismuth than when an arsenobenzol was used alone, even if it were followed by a course of one or other of the heavy metals (87). But it is rather interesting that when used in this way bismuth showed no great

1. The "aggregate" toxicity may be increased as in nephritic complications, where the excretory organs are not able to deal with the two poisons; but the "individual" toxicity of each is not increased by dual therapy.

precedence over mercury in Harrison's cases although most authorities prefer it (88).

Routes of administration and Preparations of
Bismuth.

For practical purposes Bismuth can only be given by one route, viz. intramuscularly. By inunction and by mouth it is therapeutically inactive in Syphilis, and even Levaditi admits that it is far too dangerous to give it intravenously (89).

The majority of bismuth preparations can be classified as follows:-

- (a) Water-soluble.
- (b) Water-insoluble, including metallic bismuth.
- (c) Fat-soluble.

Dealing with the first two of these, syphilologists agree with Lees in their unqualified preference for the latter for routine use. Apart from the comparatively few numbers of injections necessary the effect usually required of bismuth is a slow, steady antitreponemal action, which is excellently performed by the slow absorption of intramuscular depots of the insoluble compounds, and there is no accumulative action if a sufficiently long interval is allowed between doses (90). The water-soluble preparations in comparison appear to have no therapeutic advantage and necessitate increased inconvenience and expense to the patient.

Moore considers their use acceptable only in the rare instances where a rapid action is required and the adoption of the arylarsonates for some reason or other is inadvisable (91).

The introduction of the fat-soluble compounds is of too recent date for them to have won their spurs in syphilo-therapy, although Levaditi, one of their originators, believes them to be superior to any of the suspended preparations, and describes their action as being in two phases, the first where the fat-soluble derivative is absorbed rapidly in its existing state, and the second, prolonged over a period of weeks or months, where the bismuth is dissociated from the fat. The theory behind this is, of course, to obtain the dual effect of rapidity of action and continued activity in the one drug, but as far as I know the work has not been fully substantiated, nor is it generally accepted (92).

Toxicology of Bismuth.

Some of the untoward reactions described in the section on the Arylarsonates have been recorded following bismuth therapy and include mild Herxheimer Reactions, skin eruptions of all types, and possibly mild jaundice; bismuth as an aetiological factor in the last of these is very doubtful, and Moore states that he has never seen a case unless the patient had previously received

treatment with an arsenical; and further, that bismuth can be continued with impunity subsequent to recovery (93).

Stomatitis and Gingivitis are probably I think, the most troublesome of these complications in practice; they are seen more commonly in the hospital class of patient, whose attention to dental hygiene is not always as meticulous as it might be, and it is apparently due to bismuth being converted into a comparatively insoluble and irritating Bismuth Sulphide in the mucosa of the mouth, where H_2S is being produced as a result of dental sepsis and caries. Serious ulceration should not occur if proper care is taken throughout the treatment (94), and speedy recovery is the rule in my experience when the administration of the drug is stopped. Toxic reactions on the kidney are, as in the case of the arylarsonates, comparatively rare and not nearly so serious as those resulting from mercury; difficulty might, in some cases, be experienced in differentiating such an albuminuria from a syphilitic nephritis but if on its occurrence the drug is stopped with consequent urinary improvement, one might safely ascribe its aetiology to the therapy and not the disease; and conversely (95). Of course many cases will be obvious clinically, as in those developing an albuminuria on the completion of a terminal course of bismuth where the Wassermann Reaction has remained negative from the start.

Gastro-enteritis, polyneuritis, bismuth "grippe", and general constitutional symptoms after prolonged therapy such as asthenia, anaemia, malaise, etc., are described throughout the literature, but they are common enough symptoms following many drugs, especially if they are continued over a long period, and are of the heavy metal type. All complications due to bismuth, apart from local reactions at the site of injection resulting from faulty technique, are extremely rare, if the drug is given in ordinary therapeutic doses. The exception to this is, perhaps, stomatitis, but after all this is usually a very minor disturbance and on the whole it may be said that bismuth is one of the safest forms of treatment known for Syphilis (96).

Throughout this section I have dealt with the more important of the points conducive to argument in the therapy of Syphilis with the arylarsonates and bismuth. If I were asked to draw a moral lesson from a perusal of these pages (which, I admit, is something of an anomaly in a thesis of this type) I trust they would offer a widow's mite to the evidence in favour of that old adage that wisdom is but an increased appreciation of ignorance, Thus if we take syphilology as an

example, given the clinical picture of the disease, we seek a treatment; given a treatment, we wonder how it acts and discover its complications; given its complications, we ponder the mechanism of their production; and so on, ad infinitum, with legionary collaterals, the eternally stimulating human questions of "how?" and "why?", which kindle intellectual fuel, not only for syphilological and general medical investigations, but for the whole progressive future of mankind.

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Section 5.

CASES.

The following cases were treated in the Out-patient Department of St. Paul's Hospital, Endell Street, W.C.2., during the period of my residency.

They are graded according to the stage of the infection and the symbols used are as follows:-

- Sy.1. - Sero-negative primary Syphilis.
Sy.1A. - Sero-positive primary Syphilis.
Sy.2. - Secondary Syphilis. (i.e. showing secondary
manifestations.)
Sy.3. - Tertiary or latent Syphilis.
Sy.3A. - Neuro- Syphilis.

The arylarsonate preparations employed were in the main Neokharsivan (N.K.), Stabilarosan (Stab.), Sulfarsenol (Sulf.), Silver-Salvarsan, and Tryparsamide (Tryp.).

When Stabilarosan and Sulfarsenol were administered they were usually given in alternate weekly doses, the former intravenously and the latter intramuscularly.

The term "Arsenical" has been used to denote an aggregate of arylarsonate preparations administered over a given period; Tryparsamide however has not been included under this collective term.

Bismuth (Bi.) was employed intramuscularly

in an insoluble preparation - in the majority of cases metallic Bismuth. It was usually given in conjunction with arylarsonate therapy.

Many of the cases received Mercury by mouth and Potassium Iodide, but such therapy has not been considered to have influenced our inquiry unless otherwise stated.

Particular attention has been paid to the effect of treatment on the Wassermann Reaction, and remarks of individual interest have been added to each case.

Case 1.

Sy.1.

Male. Age 29.

Admitted 2nd June, 1930.Suffering from Preputial Ulcer. Duration 2 days.On. Exam. D.G. Trep. Pallid. positive W.R. Neg.Received up to 12th. Sept. 1933.

9.3 Gms. N.K., 4.5. Gms. Stab., 5.04 Sulf -
 18.84 Gms. "Arsenical"
 and 10.8 Bi.

During 9 months, patient failed to attend for treatment when he had completed about half of this. W.R. remained negative throughout.

Remarks:- Illustrates the advisability of continuing treatment over a longer period when there has been a break in the middle of it.

Case 2.

Sy.1.

Male.

Admitted 22nd. Mar. 1928.

Suffering from Small Multiple Preputial Ulcers -
 slight induration - no areola - no
 adenitis or skin rash or other lesions.

On. Exam. D.G. no Trep. pallid. on three exams.
 W.R. \pm - . On provocative injection W.R.
 neg.

Readmitted April 1930. suffering from small abrasion on corona, no induration, adenitis present, duration ten days, no rash.
 D.G. of sore, Trep. Pallid. positive.
 W.R. negative.

Received up to Sept. 1930.

4.95 Gms. N.K.

4 " Bi.

In Sept. 1930 patient developed Jaundice; therefore Bi. only given for next two months, when N.K. resumed with no ill effects.

Received in all up to 27th January, 1931.

6.25 Gms. N.K.

8 " Bi.

W.R. remained negative throughout and on repeated examination up to Nov. 1933, without further treatment.

Remarks Note differential diagnosis of similar Chancres; also Jaundice developing during treatment. Fairly satisfactory case - the W.R. remaining negative for approx. 3 yrs. with no treatment.

Case 3.

Sy.?.

Male. Age 39.

Admitted 27th April. 1928.

History Said to have suffered from Syphilis (sore throat and rash in Feb. 1926). Had eight injections from private Doctor, ending in March 1927; has had mercury by mouth for three weeks more. No symptoms since.

On. Exam. W.R. negative. even on provocative.

Received up to 7th September 1928

2.7 Gms. Stab., 3 Gms. Sulf - 5.7 Gms. "Arsenical"

2.8 " Bi.

W.R. remained negative after treatment until 31st. Janry. 1933, on repeated examination.

Remarks - Illustrates unsatisfactory method of treating patient without proper record of case. Patient quite possibly never had Syphilis: certainly the W.R. has remained negative over a period of $4\frac{1}{2}$ years with apparently very little treatment.

Case 4.

Sy 1.

Male age 36.

Admitted 19th August 1930.

Penile Chancre - duration 13 days. Slight adenitis.

Exam. D.G. Tr. Pallid. positive.

W.R. \pm \pm

Received up to 15th Oct. 1930 2.7 Gms. N.K.
and 2.2 " Bi.

In October 1930 patient developed Jaundice, lasting for about one month; specific treatment stopped but Bi. treatment recommenced alone on 19th November 1930 and continued until 28th January 1931, when W.R. was still negative.

Received between 27th Febry. and 27th May, 1931.

2.25 Gms. Stab.
and 2.7 " Bi.

No Jaundice.

No treatment between then and 11th. December, 1931.

W.R. remaining negative on repeated examinations.

Received between 11th. December 1931 and 13th May 1932

2.1 Gms., 1.68 Gms. Sulf. - 3.78 Gms. "Arsenical"

4.84 " Bi.

W.R. remained negative up to 3rd Febry. 1933 without further treatment.

Remarks:

A satisfactory case on the whole, showing how Bismuth alone can control the W.R.; he received very little "Arsenical" for first 5 months of his infection yet W.R. still remained negative.

Case 5.

Sy. 1.

Male aged 39.

Admitted 17th July, 1930.

Suffering from Typical Chancre on Dorsum - duration ten days, inguinal adenitis present.

Exam. D.G. Tr. Pallid. positive, W.R. (\pm -).

Received during first three months 5.55 Gms. Stab.

and 2.8 " Bi.

thereafter received for next 18 months -

4.5 Gms. Stab. and 3.36 Gms. Sulf. = 7.86 Gms
"Arsenical"

and 5.8 Gms. Bi.

therefore in all he received 13.4 " "Arsenical"

and 8.6 " Bi.

in a period of 2 years.

The W.R. remained negative throughout and up to January 1935 without further treatment.

Remarks:

A well treated case of sero-negative primary Syphilis with intensive treatment at the outset, there is every possibility of permanent cure.

Case 6.

Sy. 1.

Male aged 48.

Admitted 24th. March, 1930

Suffering from Typical Penile Chancre - duration two weeks - Inguinal Adenitis present.

Exam. D.G.: - Trep. Pallid. positive. W.R. negative.

Received up to June 16th. 1930 3.8 Gms. N.K.

and 2. " Bi.

June 23rd. 1930 W.R. Negative.

Received between 14th. July, 1930 and 2nd. Dec. 1930

3.2 Gms. Bi.

Small total dosage because interrupted by Gingivitis.

Received between January 1931 and March 1931 -

4.8 Gms. N.A.B.

and 2.9 " Bi.

W.R. remained negative throughout.

Received in all 8.6 Gms. "Arsenical"

and 8.1 " Bi.

W.R. remained negative up to December 1933 without further treatment.

Remarks:

Has not received much treatment, but never the less is fairly well assured of complete cure

(W.R. has remained negative for approximately 4 years without treatment). Note fairly intensive treatment at outset.

Case 7.

Sy. 1.

Male aged 23.

Admitted 16th. January 1924.

Suffering from Coronal Chancre and Inguinal Adenitis.

Exam. D.G.:— Tr. Pallid. positive; W.R. negative.

Over a period of five years patient treated intermittently with Sulf. and Stab. (usually given in individual courses) and Bi., receiving in all 13.74 Gms. Sulf. and 10.55 Gms Stab. = 24.29 Gms "Arsenical"

and 3.2 Gms. Bi.

W.R. remained negative throughout.

7 months after last injection patient developed typical primary penile chancres in fresh situation.

On Exam. D.G. Tr. Pallid. positive; W.R. negative.

Received usual course of treatment over period of two years. W.R. remained negative throughout and 3½ years after cessation of treatment.

Remarks:→ After the too enthusiastic initial treatment with W.R. negative throughout, the second Chancre was almost certainly a new infection and not a recidive. Patient most probably "cured" in first place.

Case 8.

Sy. 1.

Male aged 27.

Admitted 29th July, 1929.Suffering from Typical Preputial Ulcer Inguinal
Adenitis present.On Exam. D.G. Tr. Pallid. positive W.R. $\frac{+}{-}$ -Received up to 18th August, 1930, with periodic
rests15 Gms. Stab.
7.6 " Bi.W.R. negative. throughout and until April, 1933 with
no further treatment.Remarks:- An uneventful, well-treated case, remaining
negative serologically for three years
(approximately) after cessation of treatment.Case 9.

Sy. 1A.

Male aged 23.

Admitted 3rd June, 1929.Suffering from Indurated area in Coronal Sulcus to
left of Fraenum - Adenitis right groin -
enlargement of epitrochlear glands - no
skin rash.On Exam. W.R. + + .Received up to 19th Sept. 1929.2.7 Gms. Stab. and 2.1 Gms. Sulf. - 4.8 Gms. "Arsenical"
and 2.8 " Bi.W.R. then negative. Continued treatment with N.A.B.
compounds and Bi. until 5th June, 1930.

W.R. remained negative throughout and until 18th.

June, 1931 (one year after cessation of treatment).

Remarks:- After 4.8 Gms. "Arsenical" and 2.8 Gms. Bi.
W.R. was reversed and remained negative.

Case 10.

Sy.1A.

Male aged 28.

Admitted 8th September 1930.

Suffering from Typical Penile Chancre and Inguinal
Adenitis.

On Exam. D.G. Trp. Pallid. positive; W.R. + ±

Received up to 17th November 1930.

1.35 Gms. N.K. 3 Gms. Stab. - 4.35 Gms "Arsenical"
and 2.5 " Bi.

W.R. then negative, thereafter received fairly
intensive treatment with "914" and Bi. until 27th.

July, 1931 7.8 Gms. Stab.

and 4.8 " Bi.

During second year Sulf. and Stab. were administered
alternately in weekly doses, in courses of three
weeks with two months interval between.

W.R. remained negative throughout and for three years
after cessation of treatment.

Remarks: After 4.3 Gms. "Arsenical" and 2.5 Gms. Bi.
W.R. was reversed to negative. A sero-
positive case of primary Syphilis in which
a "cure" might be considered assured.

Case 11.

Sy. 1A.

Male aged 30.

Admitted 13th January 1927.Suffering from Typical Hunterian Chancre - duration
one month - Inguinal Adenitis present.On Exam. D.G. Trep. Pallid. positive; W.R. + + .Received up to 24th March, 1927.2.25 Gms. Stab. 1.68 Gms. Sulf - 3.93 Gms "Arsenical"
and 1.8 " Bi.W.R. then (\pm -).

28th Janry. 1927 to 14th July, 1927 - 1.66 Gms. Sulf.

8th Sept. 1927 to 29th Sept 1927 - 1.66 " "

12th Janry. 1928 to 2nd. Febry. 1928 1.66 " "
and 1 " Bi.

28th March 1928 to 10th May 1928 - 2.1 Gms. Bi.

14th June 1928 to 5th July 1928

.9 Gms. N.K. .84 Gms. Sulf - 1.74 Gms. "Arsenical"
.8 " Bi.

3rd. Janry, 1929 to 24th Janry. 1929 1.8 Gms. Stab.

19th Sept. 1929 to 24th. Oct. 1929 1.2 " Bi.

W.R. remained negative throughout and until Janry.

1933 without further treatment.

Received in all 14.25 Gms. "Arsenical"
and 7.7 " Bi.over a period of $2\frac{1}{2}$ years.Remarks:- After 3.93 Gms. "Arsenical" and 1.8 Gms.Bi. W.R. was reversed to negative. The case was
treated fairly intensively at first and very short
but frequent courses given thereafter. A satisfactory
method as is shown, but requiring a co-operative
patient.

Case 12.

Sy.1A.

Male aged 25.

Admitted 29th July, 1930.Suffering from - Two undurated penile Chancres -
duration three weeks - no adenitis or skin lesions.On Exam. W.R. + + .Received up to 6th Nov. 1930.2.7 Gms. Stab. 2.5 Gms. Sulf - 5.2 Gms. "Arsenical"
and 2.8 " Bi.

when W.R. was reversed to negative.

Thereafter received up to 4th February 1932 -

1.8 Gms. Stab. and 1.68 Gms. Sulf - 3.48 Gms "Arsenical"
and 4 " Bi.W.R. remained negative throughout and was negative
on six-monthly inspection up to Sept. 1934.

Remarks:- After 5.2 Gms. "Arsenical" and 2.8 Gms. Bi.

W.R. was reversed to negative. Patient did
not receive a great deal of treatment, yet
reacted well, remaining serologically negative
over a period of $2\frac{1}{2}$ yrs. after cessation of
treatment.Case 13.

Sy.1A.

Male aged 24.

Admitted 5th Sept. 1929.Suffering from Typical Chancre on Dorsum with slight
inguinal adenitis. Duration two weeks.On Exam. W.R. + + .

Received.

2.7 Gms. Stab. and 2.52 Gms. Sulf -
5.22 Gms. "Arsenical"
and 2.8 " Bi.

when W.R. was negative.

Treatment continued for 2 yrs. when patient had received in all

6.75 Gms. Stab. and 8.32 Gms. Sulf -
15.07 Gms "Arsenical"
and 8 " Bi.

W.R. remained negative on repeated examinations up to May, 1935, with no further treatment.

Remarks:- W.R. was reversed to negative after 5.22 Gms.
"Arsenical" and 2.8 Gms. Bi.

Case 14.

Sy. LA.

Male aged 41.

Admitted 1st May, 1930.

Suffering from Typical Hard Chancre and Inguinal
Adenitis -

Previous History - of Penile sore and inguinal Bubo
eight years ago - received two courses of
N.A.B. and Hg. W.R. negative on two
occasions 4 years ago.

On Exam. D.G, Tr. Pallid. positive. W.R. + + .

Received up to 29th July, 1930 -

2.7 Gms. Stab. and 2.52 Gms. Sulf. -
5.22 Gms "Arsenical"
and 3 " Bi.

W.R. then reversed to negative.

Did not attend for another year, but W.R. still negative.

Received between August, 1931 and March, 1933 -

1.6 Gms. Stab and .82 Gms. Sulf. - 2.42 Gms. "Arsenical"

and 1.2 " Bi.

W.R. remained negative throughout and on repeated examination without further treatment until March, 1935 i.e. 3 years after cessation of treatment.

Remarks:- Note W.R. remained negative for one year after 5.22 Gms. "Arsenical" and 3 Gms. Bi. although Patient had no further treatment. Note also the possibility that this was the second attack of Syphilis.

Case 15.

Sy.1A.

Male aged 27.

Admitted 13th March, 1930.

Suffering from -Large Chancre on fraenum - duration seven days - inguinal adenitis present.

On Exam. D.G. Trep. pall. positive. W.R. + + .

Received

2.25 Gms. Myosalvarsan and 3.15 Gms. Stab. -
5.4 Gms. "Arsenical"

and 3 " Bi.

when W.R. was negative.

Received further treatment, but did not complete first year's course.

Remarks:- After 5.4 Gms. "Arsenical" and 3 Gms. Bi. W.R. was reversed to negative.

Case 16.

Sy.2.

Male aged 42.

Admitted 17th Sept. 1929.Suffering from Typical Chancre - inguinal and general adenitis and roseolar rash.On Exam. W.R. + + .Received in next 14 weeks -

2.7 Gms. Stab. and 2.52 Gms. Sulf -
 5.22 Gms. "Arsenical"
 and 3 " Bi.

when W.R. was reversed to negative.

31st Dec. 1929 - patient developed Jaundice
 (i.e. a few days after cessation of treatment).

Jaundice cleared within a month. Resumed treatment
 on 11th. March, 1930 with Bi. alone for the next six
 months.

Receiving - 4.2 Gms. Bi.

W.R. remained negative.

Thereafter continued treatment with Stab. and Sulf.
 and Bi. with no return of Jaundice.

Remarks:- After 5.22 Gms. "Arsenical" and 3 Gms. Bi.

W.R. was reversed to negative. Note the
 occurrence of Jaundice, soon after previous
 injection of "Arsenical". Note how Bi. has
 controlled W.R. over a period of six months.

Case 17.

Sy. 2.

Male aged 36.

Admitted 4th July, 1928.

Suffering from Indurated preputial Ulcer
 Inguinal and general adenitis.
 Diffuse macular rash.

On Exam. W.R. + + .Received up to 29th November, 1928.

2.7 Gms. Stab. and 2.52 Gms. Sulf - 5.22 Gms "Arsenical"
 and 2.6 " Bi.

when W.R. was reversed to negative.

Thereafter continued similar treatment until 9th.
 of October, 1930, the W.R. remained negative throughout
 and up to 14th April, 1932, on repeated examination
 without further treatment.

Remarks:- After 5.22 Gms. "Arsenical" and 2.6 Gms.
 Bi. the W.R. was reversed to negative.

Case 18.

Sy. 2.

Male aged 29.

Admitted 14th August, 1928.

Suffering from Typical ulcer on glans
 General adenitis
 Generalised florid rash.

On Exam. D.G. Tr. Pallid. positive.
 W.R. + + .

Received up to 3rd December, 1928 -

1.35 Gms. N.A.B. and 3.18 Gms. N.K. -

4.53 Gms. "Arsenical"

and 2 " Bi.

when W.R. was negative.

The patient had no other treatment until 31st March, 1930, when he developed adenitis of both groins and the W.R. was strongly positive. It had been negative up till then on six monthly inspection i.e. there was serological relapse after fifteen months.

Received between April and August, 1930 -

.84 Gms. Sulf and .45 Gms. N.K. - 1.29 Gms. "Arsenical"

and 2 " Bi.

The W.R. was then negative and remained so without further treatment until September, 1932 i.e. two years.

Remarks:- The W.R, was reversed to negative after 4.53 Gms. "Arsenical" and 2 Gms. Bi. but relapsed after fifteen months, It was easily reversed again after 1.29 Gms. "Arsenical" and 2 Gms. Bi. and remained so for two years without further treatment. The patient was suffering from acute eczema of the perineum (which was the cause of the adenitis in the groin?) hence meagreness of treatment.

Case 19.

Sy. 2.

Male aged 19.

Admitted 24th September, 1928.

Suffering from - Typical Hunterian Chancre (almost healed)

Generalised rash.

On Exam. D.G. no Trep. Pallid. found.

W.R. + ±

Received up to 21st. January, 1929.

1.56 Gms. Sulf and 2.2 Gms N.K. - 3.76 Gms. "Arsenical"

and 1.6 " Bi.

The W.R. was then negative.

No further treatment given and W.R. remained negative until 19th December, 1929 i.e. eleven months, when W.R. was ± and + + on provocative injection.

The W.R. was again reversed to negative after two injections of .45 Gms. N.K. and .4 Gms. Bi.

N.K. and Bi. therapy continued until July 1930, the W.R. remaining negative without further treatment, until September, 1932, on repeated examination.

Remarks:- After 3.76 Gms. "Arsenical" and 1.6 Gms. Bi. the W.R. was reversed to negative, but relapsed after eleven months, no treatment being given. It was easily reversed again after .9 Gms. N.K. and .4 Gms. Bi. Note effect of provocative.

Case 20.

Sy. 2.

Male aged 42.

Admitted 23rd. July, 1930.

Suffering from Condylomata lata around anus.
(two months)
Mucous patch at junction of lips
No history of Chancre.

On Exam. D.G, of Condylomata, Trep. Pallid. positive.

W.R. + + .

Received in next two months - 3.9 Gms. N.k.

and 4 " Bi.

W.R. then negative.

Received until 7th April, 1931, two further courses of "914" and Bi.

In all 11.4 Gms. "Arsenical"
and 10.2 " Bi.

No "Arsenical" treatment between 7th April and 19th May, 1931, i.e. six weeks, when he developed Jaundice with bile in urine which took two months to clear. Continued treatment in September, 1931, with usual intermittent courses of "Arsenical" and Bi. with no ill effects.

W.R, remained negative throughout and from June, 1932 to May, 1935 i.e. 3 years with no further treatment.

Remarks:- The W.R. was reversed to negative after 3.9 Gms. N.K. and 4 Gms. Bi.

Note the development of Jaundice six weeks after the last injection of "Arsenical". In view of intensive treatment previously, this was hardly likely to be a recidive, and was most probably due to the drug. (vide section 4, Post-Salvarsan Jaundice).

Note diagnostic value of Condylomata lata.

Case 21.

Sy. 2.

Male aged 23.

Admitted 17th June, 1930.

Suffering from - General Adenitis

Maculo-papular rash, (duration eight weeks.

Chancre five months previously.

On Exam. W.R. + + .

Received up to 30th Sept. 1930.

2.7 Gms. Stab and 2.52 Gms. Sulf - 5.22 Gms "Arsenical"

and 2.9 " Bi.

W.R. then reversed to negative.

Thereafter received up to June, 1932.

3.78 Gms. Sulf and 3.15 Gms. Stab. - 6.93 Gms "Arsenical"

and 5 " Bi.

In all, in a period of two years received

12.15 Gms. "Arsenical"

and 8 " Bi.

W.R. remained negative throughout and up to January, 1934.

Remarks:- W.R. reversed to negative after 5.22 Gms.

"Arsenical" and 2.9 Gms. Bi. in spite of long duration of Syphilis. An uneventful case well treated.

Cases 22.

Sy. 2.

Male aged 36.

Admitted 3rd April, 1930.

Suffering from Penile Chancre.

General Adenitis.

Generalised Papular Rash.

Previous history - Syphilis eight years previously,

when he was treated with six injections of ?

"914" and Hg. pills for eight months.

On Exam. W.R. + + .

Received up to August 1930.

2.7 Gms. Stab. and 2.52 Gms. Sulf.
 = 5.22 Gms. "Arsenical"
 and 1.6 " Bi.

When W.R. was negative.

Received only three other injections and failed to attend.

Remarks:- The W.R. was reversed to negative after 5.22 Gms. "Arsenical" and 1.6 Gms. Bi. Note the possibility of this being a second attack of Syphilis.

Case 23.

Sy. 2.

Male aged 35.

Admitted 18th. February 1929.

Suffering from - Typical Penile Chancre.
 Inguinal Adenitis
 Diffuse maculo-papular Rash.
 Ulcer of hard palate.

On Exam. W.R. + + .

Received up to 18th. June, 1929 -

1.95 Gms. N.A.B. and 3.48 Gms. Sulf. =
 5.43 Gms. "Arsenical"
 and 1.8 " Bi.

when W.R. was negative.

Up to August, 1930, the patient only received a further .45 Gms. N.K. and 4 Gms. Bi.; yet W.R. remained negative throughout and for 2½ years afterwards without further treatment.

Remarks:- After 5.43 Gms. "Arsenical" and 1.8 Gms.

Bi. the W.R. was reversed to negative, and remained so with very little further "Arsenical" treatment; the initial course it may be noted was fairly intensive.

Case 24.

Sy. 2.

Male aged 42.

Admitted 23rd. July, 1930.Suffering from Condylomata lata around anus.

Mucous patch round mouth, duration
two months.

On Exam. D.G. of Condylomata, Trep. Pallid. positive.

W.R. + + .

Received up to 23rd Sept. 1930 - 3.9 Gms. N.K.

and 4 " Bi.

when W.R. was negative;

Continued further courses of treatment, receiving
in all, over a period of two years

16.73 Gms. "Arsenical"

and 16.6 " Bi.

After the first nine months of treatment, when
patient had received 11.45 Gms. N.K.

and 10.4 " Bi.

he developed Jaundice five weeks after the previous
injection. Jaundice lasted about one month and
the patient was able to continue treatment ten weeks
later with no ill effects.

Remarks:- W.R. was reversed to negative after 3.9
Gms. N.K. and 4 Gms. Bi. Note the occurrence
of Jaundice five weeks after previous injection.

Previous "Arsenical" therapy had been somewhat "heroic".

Case 25.

Sy. 3.

Male aged 26.

Admitted 23rd August, 1927.

Suffering from Condition other than Syphilis.

Previous history Gonorrhoea Syphilis in 1922, partially treated,

On Exam. no clinical symptoms. Routine W.R. + + .

Received between 5th October, 1927 and 20th.

December, 1927.

.8 Gms. Silver-Salvarsan and 3.9 Gms. N.K. -

4.7 Gms. "Arsenical"

and 1.6 " Bi.

The patient failed to attend again until 12th.

June, 1928 i.e. six months later, when W.R. + + .

Received in next four years (very irregularly)

1.8 Gms. N.K. and 2.64 Gms. Sulf - 4.44 Gms. "Arsenical"

and 6 " Bi.

when W.R. was reversed to negative for first time.

W.R. remained negative for next two years without further treatment.

No signs of Syphilis throughout.

Remarks:- Apparently a fairly easily reversed W.R.

considering the duration of the Syphilis (five years). An unsatisfactory type of patient, but seems to have done fairly well even on very irregular treatment.

Case 26.

Sy. 3.

Male aged 63.

Admitted 6th March, 1930.Suffering from Condition other than Syphilis
(Prostatic Calculi).Previous history Syphilis in 1918 i.e. 12 years
previously, when he had 20 injections
of N.A.B. and Hg.On Exam. The only sign that might be syphilitic was
superficial glossitis.

W.R. negative.

Treated for prostatic condition until 26th September,
1933, when W.R. was taken and found to be + + . even
on repetition -Received between Sept. 1930 and December 1933 -
i.e, 3 years.5.88 Gms. Sulf and 6.3 Gms. Stab. - 12.18 Gms "Arsenical"
and 4.6 " Bi.

when W.R. was + for first time.

No definite signs of Syphilis throughout.

Remarks:- Note the relapse in the W.R. with apparently
no clinical signs or symptoms to account for
it. The treatment was given in courses of
three or four weeks with long intervals (two
months) between because the patient was

1. An elderly man.

2. Was in poor condition.

due to prostatic calculi.

Case 27.

Sy. 3.

Male aged 56.

Admitted 23rd September 1930.Suffering from Irido-cyclitic of left eye.

duration - ten days.

Previous history Syphilis two years ago - no treatment.On Exam. W.R. + + .Received up to 4th December, 1930

2.1 Gms. Sulf. and 1.8 Gms, Stab. -

3.9 Gms. "Arsenical"

and 2.2 " Bi.

when Jaundice developed immediately subsequent to injection of "Arsenical"; cleared in eight weeks.

W.R. reversed to negative.

Treatment with Bi. recommenced in March, when patient received two injections only.

Failed to attend until July, 1931 when eye condition had relapsed although W.R. was negative.

Bi. treatment continued but developed Gingivitis; therefore, treatment carried on with Hg. by mouth, (and very occasional injections of Bi). until December, 1932.

W.R. negative throughout and eye condition cleared.

W.R. remained negative for next $2\frac{1}{2}$ years with no further treatment; no signs of Syphilis meanwhile.

Remarks:- Illustrates how Mercury alone, if taken regularly, by mouth can keep syphilitic infection under control.

Case 28.

Sy. 3.

Male aged 63.

Admitted 8th April, 1930.Suffering from Condition other than Syphilis.
(Inguinal Hernia).Previous history Syphilis 30 years ago.

Apparently no treatment.

On Exam. No symptoms or signs of Syphilis.

W.R. + + .

The patient was put on small weekly doses of Bi. but failed to attend after October, 1930; Written for and attended in April, 1932, when he stated that on his first attendance he felt quite well, but that after injections of Bi. his general health and suffered. He had felt better in the past year since cessation of treatment!.

W.R. + + .

Received occasional injections on "914" and Bi. up to June, 1934.

W.R. continued + + .

Remarks:- Note long duration of Syphilis with positive W.R. but no physical signs or symptoms. A case I think which on the whole should have been kept under observation but not treated. One is dealing with a patient and not a Wassermann Reaction.

Case 29.

Sy. 3.

Male aged 60.

Admitted 22nd October, 1929.Suffering from Vague pains in the body.

Previous history Syphilis in 1900 - treated for
 six months at the time and also
 from 1919 to 1923 with numerous
 injections.

On. Exam. No physical signs or symptoms of Syphilis.
 Old scarring on body.

W.R. + + .

The patient has been treated to date and received in
 all, over a period of six years, 32 injections of
 "Arsenical" and 61 injections of Bi. in addition to
 Iodides and Mercury by mouth.

During all this time W.R. has remained strongly
 positive, but there has been no physical signs of
 Syphilis.

Remarks:- A clear case of Wassermann "fastness"
 creating a syphilophobia (the patient was a
 most regular attendant). Off and on for 35 years
 the patient has been treated for Syphilis
 which has shown no clinical sign or symptom
 since its onset - which on the face of it is
 scientific medicine ran amok.

Case 30.

Sy. 3.

Male aged 60.

Admitted 2nd January 1929.Suffering from Swelling of lips and numbness of feet.Previous history Syphilis 38 years previously, treated only with "medicine"On Exam. No evidence of Syphilis clinically.

W.R. + + .

C.S.F. no abnormalities.

Received over a period of $4\frac{1}{2}$ years 20 Gms "Arsenical" and 12.2 " Bi.

W.R. remained + + throughout.

Had slight Jaundice occurring six months after treatment had commenced and just subsequent to an injection of "Arsenical"; cleared in a fortnight.Remarks: The case illustrates Wassermann "fastness" with no apparent ill effects to the patient, (he sustained Nephrectomy operation for Pyonephrosis during the above treatment).Case 31.

Sy. 3.

Male aged 24.

Admitted 13th February, 1926.Suffering from Condition other than Syphilis.Previous history nil.On Exam. No physical signs or symptoms of Syphilis
Routine W.R. + + (June 1926).Received in a period of two years -

13 Gms. "Arsenical"

and 8.5 " Bi.

when W.R. was completely negative for first time.

W.R. remained negative until 1933 on repeated examination without further treatment (5 years).

Remarks:- Note the large amounts of "Arsenical" and Bi. required to reverse the W.R. once the secondary stage is passed without treatment. The case was, however, a satisfactory one in the long run as is shown by the long period over which the W.R. was negative without treatment.

Case 32.

Sy. 3.

Male aged 44.

Admitted 17th September, 1929.

Suffering from Preputial sore.

Previous history Syphilis 24 years ago; no treatment

On Exam. D.G. of sore, Trep. Pallid. not present i.e. sore probably innocent.

W.R. + + .

Received up to July, 1933 i.e. 4 years.

8.52 Gms. Sulf. and 9.4 Gms. Stab. -
17.92 Gms. "Arsenical"

and 10.2 " Bi.

W.R. remained + + throughout.

C.S.F. no abnormalities.

No clinical signs or symptoms of Syphilis.

Remarks:- A clear case of Wassermann "fastness" with no inconvenience to the patient.

Case 33.

Sy. 3.

Male aged 51.

Admitted 23rd May, 1929.Suffering from Seborrhoeic Eczema (non-syphilitic)Previous history - indefinite - no treatment.On Exam. No physical signs or symptoms of Syphilis.

W.R. + + .

Received up to 12th December, 1929 i.e. 7 months.

3.15 Gms. Stab. and 3.24 Gms. Sulf -

6.39 Gms. "Arsenical"

and 3.4 " Bi.

W.R. remained++ .

On 21st December, 1929, patient underwent operation for Perforated Gastric Ulcer and did not attend until June, 1931.

W.R. then found to be negative and remained so for next two years on repeated examination and following provocative injection.

C.S.F. no abnormalities.

Remarks:- Note the reversal of the W.R. 18 months after cessation of treatment although it was strongly positive immediately after a fairly intensive course of "Arsenical" and Bi. The reversal was moreover maintained for a further period of two years. An explanation for this is difficult unless we presume that laboratory technique was at fault.

Case 34.

Sy. 3A.

Male aged 27.

Admitted 26th June, 1930.Suffering from Papular syphilide of tongue.

Hypertrophic syphilides at angle of
mouth - no evidence of C.N.S.
involvement.

Previous history Syphilis in 1925 - received 16
injections N.A.B. and sixteen of Hg.
W.R. negative at termination of course
in 1926 - no treatment since.

On Exam. W.R. + + .C.S.F.-W.R. (\pm -) (- -) (- -) (- -)

Cells - 6.6 p. cmm.

Glob. - faint trace.

Lang. oooooooooo.

Received up to 23rd September 1930.

2.52 Gms. Sulf. and 2.7 Gms. Stab.

5.22 Gms. "Arsenical"

and 2.6 " Bi.

W.R. Reversed to negative.

Received between January, 1931 and December 1931 -

2.52 Gms. Sulf. and 1.8 Gms. Stab.

4.32 Gms. "Arsenical"

and 1.8 " Bi.

W.R. remained negative throughout.

Received between November 1932 and December 1932 -

1.35 Gms. Stab.

and .6 " Bi.

W.R. remained negative until October, 1933, when it
relapsed to \pm and Kahn was + + + +.

C.N.S. - W.R, (++) (+-) (- -) (- -)

Cells 21.6 p. cmm.

Glob. - present.

Lange - 11111 00000.

Received in following year - 27 Gms. Tryp.

and 2.2 " Bi.

W.R. negative.

C.N.S. - W.R. (- -) (- -) (- -) (- -)

Cells 6 p. cmm.

Glob. - positive.

Lange.- 11111 00000

Receiving Tryp. and Bi. therapy to date.

Remarks:- Note (1) Hypertrophic syphilides as
recidives.

(2) C.S.F. relapse even after
continuous treatment.

(3) Effect of Tryparsamide on
abnormalities of C.S.F.

Case 35.

Sy. 3.A.

Male aged 56.

Admitted 2nd May, 1929.

History Became dizzy in street $4\frac{1}{2}$ years ago and
has been treated at St. Barts. Hospital
with malaria and intensive N.A.B. courses;
has also had Tryp (?).

Previous History - Syphilis 37 years ago - treated
with pills and inunctions.

On Exam, No physical signs of Neuro-syphilis.

W.R. negative.

C.S.F. - W.R. (+ +) (+ +) (+ ±) (- -)

Cells 2.3 p. cmm.

Glob. present.

Lange 1122210000.

Received up to November 1929.

2.46 Gms. Sulf. and 1.15 Gms. Silver-Salvarsan -

3.61 Gms. "Arsenical"

and 4.5 " Bi.

W.R. negative

C.S.F. as before.

Received between January 1930 and April 1931 -

28. Gms. Tryp.

and 4.6 " Bi.

C.S.F. examination on completion of this treatment -

W.R. (+ +) (+ -) (- -) (- -)

Cells - 1. p.cmm.

Glob. present.

Lange 1111100000.

Thereafter received occasional courses of Tryp. and

Bi. up to November, 1933, when C.S.F. was as above.

Blood W.R. negative throughout.

28th November, 1933 - cerebral thrombosis with

resultant left hemi-paresis.

Remarks:- Note the practical uselessness of blood

W.R. in neuro-Syphilis and the absence of clinical signs with a positive C.S.F. The only sign of the patient's condition was retinal arterio-sclerosis with no clinical indication apart from the history of its being due to Syphilis.

Note serological benefit on C.S. F.
following Tryparsamide.

Case 36.

Sy. 3A.

Male aged 41.

Admitted 10th November, 1927.

Suffering from Condition other than Syphilis.
(Psoriasis).

Previous history - Syphilis in 1908.On Exam. No clinical evidence of Syphilis.

W.R. + + .

C.S.F. - W.R. (++) (++) (++) (+-)

Cells. 16 p. cmm.

Glob. - present.

Lange. 2221000000.

Received over a period of $5\frac{1}{2}$ years -

4.57 Gms. Sulf. and 6.75 Gms. Stab. and 4.4 Gms.
Silver Salvarsan -

15.72 Gms. "Arsenical"

and 88.5 " Tryp.

and 14 " Bi.

The C.S.F. during this treatment improved and on its
completion read:-

W.R. (- -) (- -) (--) (- -).

Cells - .6 p. cmm.

Glob. negative.

Lange 0010000000. i.e. normal.

Blood W.R.

Has received courses of Tryp. and Bi. to date with

no effect on Blood W.R.

Remarks:- Note the effect of the Arylarsonates on the C.S.F. and the "fastness" of the Blood W.R. in contra-distinction to the C.S.F. after therapy. It was not possible in this case to differentiate the most potent of the "Arsenical" preparations. The patient had no symptoms of Syphilis throughout except slight headache.

Case 37.

Sy. 3A.

Male aged 48.

Admitted 28th January, 1930.

Suffering from Incontinence of Urine.

Previous history -Syphilis, 1915. has received irregular treatment.

On Exam. Pupils normal.

K.J's absent.

Hypertr. Charcot's right ankle.

W.R. + ±

C.S.F. - W.R. + + .

Cells 63 p. cmm.

Glob. positive.

Lange 1222110000.

Received up to June 1930

2.52 Gms. Sulf. and 1.65 Gms. Silver-Salvarsan -

3.17 Gms. "Arsenical"

and 2.4 " Bi.

W.R. ± - .

Received up to 17th May, 1935 i.e. 5 years -

60.75 Gms. Tryp.

and 12.4 " Bi.

apart from treatment received at Westminster Hospital,
where patient was admitted for some time.

Ankle became progressively worse.

Remarks:- Illustrates the inability of anti-syphilitic
treatment to influence trophic lesions.

Case 38.

Sy. 2A.

Male aged 49.

Admitted 19th September, 1929.

Suffering from Retention of Urine and overflow.

Previous history - nil.

On Exam. Argyl-Robertson pupils.

No other signs of Syphilis.

W.R. + + .

C.S.F. - W.R. (+ \pm) (\pm -) (- -) (- -)

Cells 1.3 p. cmm.

Glob. - trace.

Lange 0000000000.

Received over a period of $2\frac{1}{2}$ years 65 Gms. Tryp.

and 5.2 " Bi.

Blood W.R. had then become negative.

and urinary symptoms had completely cleared up.

Seven weeks after the cessation of treatment patient
developed Jaundice from which he recovered in about

one month. Nine months after the cessation of treatment C.S.F. and Blood W.R. were negative, and urinary symptoms were completely relieved.

Remarks:- An excellent reaction of early neurosyphilis to Tryparsamide both serologically and symptomatically. Note Jaundice developing seven weeks after last injection of Tryparsamide.

Case 39.

Sy. 3A.

Male aged 54.

Admitted 2nd October, 1928.

Suffering from - Tabes dorsalis and poor vision.

Previous history - nil

On Exam. 1. Pupils, - right greater than left.

2. Double optic atrophy.

3. K.J.'s absent.

4. Incontinence of Urine, at night.

W.R. + + .

C.S.F. - W.R. (++) (++) (++) (++)

Cells 78 p.cmm.

Glob. present.

Lange 1000000000.

Received over a period of two years.

5.14 Gms. Sulf and 4.95 Gms. Stab. and 1.65 Gms.
Silver-Salvarsan.

11.74 Gms. "Arsenical"

and 27 " Tryp.

and 8.4 " Bi.

During this time W.R. was still strongly positive and at the end C.S.F. read.

W.R. (++) (++) (++) (++)

Cells 13.3 p.cmm.

Glob. trace.

Lange. 2345544210.

Optic atrophy showed no improvement and vision got worse.

Remarks:- Poor serological effect of "Arsenical" and Tryparsamide therapy on C.S.F. Wassermann and Lange's Test, but improvement in cells and glob; no arrest of optic atrophy.

Case 40.

Sy. 3A.

Male aged 43,

Admitted 13th April, 1926.

Suffering from Conjunctivitis and deafness.

Previous history- Syphilis 20 years ago. Treated for two years at time of onset. Recently attended Ophthalmic Hospital and received six injections of "914".

On Exam. No clinical evidence of neuro-syphilis.

W.R. + + .

C.S.F. - W.R. (++) (++) (++) (++)

Cells 25 p.cmm.

Glob. present.

Lange 2110000000.

Thereafter received occasional courses of Tryp. and Bi. the W.R, vacillating between doubtful and negative.

Remarks:- The case shows some effect of arylarsonate therapy on the globulin and cells of C.S.F. but little or none on W.R. and Lange's test.

Case 41.

Sy. 3A.

Male aged 48.

Admitted 25th February, 1930.

Previous history - Syphilis 19 years ago, treated with inunctions and pills. In 1928 received malarial therapy and six injections for G.P.I.(?) at West End Hospital for Nervous Diseases.

On Exam. Argyl-Robertson Pupils; no other signs of neuro-Syphilis.

W.R. $\begin{matrix} + \\ - \end{matrix}$ -

C.S.F.- W.R. (++) (+ \pm) (\pm -) (- -)

Cells 1.3 p. cmm.

Glob. present.

Lange 1122111000.

Received over a period of one year

.9 Gms. Sulf. and .75 Gms. Silver-Salvarsan -

1.65 Gms. "Arsenical"

and 44.5 " Tryp.

and 4.8 " Bi.

when W.R. was completely negative for first time and
C.S.F. read W.R. - (+ \pm) (+ -) (- -) (- -)

Cells 1.6 p. cmm.

Glob. present.

Lange 01223100000.

The following year received - 36 Gms. Tryp.
and 2.4 " Bi.

Received in all (over a period of two years)

80 Gms. Tryp.
and 6 " Bi.

W.R. remained negative for further three years on
repeated examination without further treatment and
patient's general health remained good.

Remarks:- Tryparsamide has definitely kept in check
the syphilitic process from a clinical point
of view and there is some evidence of
improvement of the C.S.F.

Case 42.

Sy. 3A.

Male aged 60.

Admitted 14th May, 1929.

Suffering from Ocular Palsy.

Previous history - Syphilis 9 years ago - no
treatment.

On. Exam. Pupils - left greater than right, but
react to light and accomodation.

Diplopia but no strabismus.

Tremor of tongue.

Speech bad as to labials.

W.R. + + .

C.S.F. - W.R. (+ +) (+ +) (+ +) (+ +).

Cells 114 p. cmm.

Glob. present.

Lange 2111100000.

Received in next seven months -

1.5 Gms. Sulf. and 1.85 Gms. Silver-Salvarsan -

3.55 Gms. "Arsenical"

and 3.6 " Bi.

and 11 " Tryp.

Refused further injections or L.P. thereafter.

W.R. positive at end of active treatment, but negative 4 years afterwards with no intermittent treatment; physical condition in statu quo.

Remarks:- An early case of G.P.I. apparently, but he had hardly enough treatment to abort the disease; general condition was not changed. Are there some cases of G.P.I. which are self abortive ? It is a pity that further C.S.F. examinations were refused.

Case 43.

Cong. Sy.

Male Aged 17.

Admitted 3rd May, 1927.

Suffering from Choroiditis - diagnosed at age of
12, but received no treatment;
vision becoming poor.

On Exam. Choroido-retinitis and optic atrophy of
both eyes.

Ext. and Sup. recti faulty in left eye.

W.R. + + .

C.S.F. no abnormalities.

Received over a period of two years -

4.3 Gms. Sulf. and 2.7 Gms. Stab. and 4.4 Gms.
Silver-Salvarsan -

11.4 Gms. "Arsenical"

and 6 " Bi.

when W.R. was negative; it had vacillated between
negative and strongly positive during this time.
Further treatment for next two years consisted of
courses of Sulf. and Stab. and Bi. during which
W.R. remained negative, and also for the next six
months without further treatment.

The Choroiditis and optic atrophy remained much the
same if anything progressed.

Remarks:- Illustrates progressiveness of optic
atrophy and the possibility of reversing the
W.R. in congenital Syphilis with perseverance.

Case 44.

Cong. Sy.

Male aged 16.

Admitted 1st May, 1930.

Suffering from Interstitial Keratitis; duration
seven years, during which he had
received treatment.

On. Exam. Opacity of both corneae.

W.R. + + .

Received to date i.e. 5 years.

8 Gms. Sulf and 9.6 Gms. Stab. - 17.6 Gms. "Arsenical"

and 14 " Bi.

W.R. ++ throughout.

Eye condition unchanged.

Remarks:- Illustrates W.R. "fastness" in congenital
syphilis.

SUMMARY OF CASES.

Particulars of 44 cases are given.

1. Cases 1 to 8 are of individual interest.
2. Sixteen cases of early sero-positive Syphilis have been described (cases 9 to 24).

In all of these the Wassermann Reaction was reversed to negative after the first course of treatment with "Arsenical" and Bismuth, the average amount of the two drugs given being 4.78 Gms. and 2.64 Gms. respectively.

3. Cases 25 to 33, in which the secondary manifestations had disappeared but which still showed a positive Wassermann Reaction required prolonged and intensive treatment before any effect on the reaction was noticed; some remained Wassermann "fast" throughout. In general terms the longer the duration of the positive Wassermann Reaction, the more prolonged and intensive was the therapy required to influence it.
4. Cases 34 to 42 were various types of neuro-Syphilis. In the majority a definite improvement was demonstrable in the abnormalities of the C.S.F. following Tryparsamide therapy.
5. Cases 43 and 44 demonstrate the "fastness" of the Wassermann Reaction in Congenital Syphilis.
6. Cases 7, 14, and 22 might definitely be considered to have been "cured" of a previous attack of Syphilis, and have acquired a second infection.

7. Among the 44 cases described 8 developed Jaundice. Of these 4 occurred during or immediately subsequent to the first course of treatment and 1 towards the end of the first half year while treatment was being administered. 2 cases occurred towards the end of the first year and 5 to 6 weeks subsequent to a previous injection of "Arsenical"; they had received approximately 11 Gms. "Arsenical".

1 case occurred following Tryparsamide after 2 years treatment, during which 65 Gms. of the drug had been administered; the Jaundice developed 7 weeks after the previous injection.

The complication was treated usually with injections of Sodium Thiosulphate and Glucose (intravenously or by mouth). In the majority of cases the Jaundice cleared within a month and in only one case lasted 8 weeks. Arsenical therapy was continued when necessary, without, harm, after an interval usually bridged by Bismuth.

The high incidence of the condition was probably due to the fact that we were dealing with patients of the poorer class whose diet was, to say the least, questionable.

GENERAL SUMMARY.

The theme of this Thesis has been discursive rather than exhaustive; statistical and technical details have been introduced in a few instances merely to illustrate generalities; we have looked at the cosmos, rather than at the atom.

In the short introduction an analogy has been drawn between Syphilis and many of the protozoal diseases as far as its clinical course and reaction to treatment are concerned.

Section 2 has dealt with the more important steps leading to the monumental discoveries of Schaudinn, Wassermann, and Ehrlich, and the subsequent development of their work has been briefly described.

We have discussed the Wassermann Reaction with regard to its mechanism and an attempt has been made to correlate the phenomenon with recognised general immunological principles and experimental data; the clinical significance of the reaction has been freely discussed and some technical modifications have been mentioned. Authoritative opinion has been quoted regarding the utility of the test compared to the precipitation procedures, and the section concludes with a word or two on the Leutin Test.

The comparative clinical and serological effects of "606" and "914" preparations have been considered, and we have dealt briefly with some of the more recent arylarsonate productions. The

complications of arylarsonate therapy have received special attention, particular reference being made to their pathogenesis. The discussion of Bismuth therapy has been dealt with similarly.

Finally in Section 5, 44 cases have been examined and a separate summary appended.
